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(54) Title:	HYDROXAMIC ACID AND CARBOXYLIC ACID DERIVATIVES, PROCESS FOR THEIR PREPARATION AND USE THEREOF	
(57) Abstract	<p>This disclosure relates to a novel class of hydroxamic and carboxylic acid based matrix metalloproteinase inhibitor derivatives. The disclosure further relates to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in the treatment of matrix metalloproteinase induced diseases.</p>	

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HYDROXAMIC ACID AND CARBOXYLIC ACID DERIVATIVES,
PROCESS FOR THEIR PREPARATION AND USE THEREOF

5

FIELD OF THE INVENTION

The invention is directed to pharmaceuticals useful in diseases characterized by unwanted matrix metalloproteinase activity.

10

BACKGROUND OF THE INVENTION

- A number of small peptide like compounds which inhibit metalloproteinase have been described. Perhaps the most notable 15 of these are those relating to the angiotensin converting enzyme (ACE) where such agents act to blockade the conversion of the decapeptide angiotensin I to angiotensin II, a potent pressor substance. Compounds of this type are described in EP-A-0012401.
- 20 Certain hydroxamic acids have been suggested as collagenase inhibitor as in U.S.A. Patent 4,599,361; WO-A-9005716 and WO-A-9005719. Other hydroxamic acids have been prepared as ACE inhibitors, for example, in U.S.A. Patent 4,105,789, while still others have been described as enkephalinase inhibitors as in 25 U.S.A. Patent 4,495,540.

The hydroxamic and carboxylic acids of the current invention act as inhibitors of mammalian matrix metalloproteinases (MMPs). The MMPs include, for example, collagenase, stromelysin and 30 gelatinase. Since the MMPs are involved in the breakdown of the extracellular matrix of articular cartilage (Arthritis and Rheumatism, 20, 1231-1239, (1977)), potent inhibitors of the MMPs may be useful in the treatment of arthritides, for example, osteoarthritis and rheumatoid arthritis and other diseases which 35 involve the breakdown of extracellular matrix. These diseases

include corneal ulceration, osteoporosis, periodontitis, tumor growth and metastasis.

The use of hydroxamic acid derivatives for the effective inhibition of the destruction of articular cartilage as a model of 5 rheumatoid and osteoarthritis has been demonstrated (Int. J. Tiss. Reac., XIII, 237-243 (1991)).

Topical application of hydroxamate inhibitors may be effective against corneal ulceration as demonstrated in the alkali-injured 10 cornea model (Invest. Ophthalmol Vis. Sci., 33, 33256-3331 (1991)).

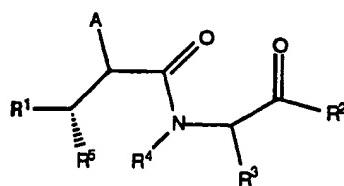
In periodontitis, the effectiveness of tetracycline has been attributed to its collagenase inhibitory activity (J. Perio. Res., 15 28, 379-385 (1993)).

Hydroxamic acid derivatives have also been effective in models of tumor growth (Cancer Research, 53, 2087-2091 (1993)) and tumor invasion (Mol. Cell Biol., 9, 2133-2141 (1989)).

20 The current invention relates to a series of hydroxamic and carboxylic acids, which act as inhibitors of matrix metalloproteinases, their preparation, pharmaceutical compositions containing them, and the intermediates involved in their 25 preparation.

SUMMARY OF THE INVENTION

This invention provides compounds which are matrix 30 metalloproteinase inhibitors. The compounds have the structure:



wherein

A is A¹ - A²- A³

A¹ is C₁₋₁₀ alkyl, C₂₋₁₀ alkene, C₂₋₁₀ alkyne having C₁₋₅ in the backbone or a chemical bond;

5 A² is X - Y- Z; wherein

X is a chemical bond, -O-, -NH-, or -S-;

Y is -CO-, or -CHR⁹; and

Z is -O-, -NH-, -S-, or a chemical bond;

10 A³ is hydrogen, C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryl C₁₋₆ alkyl, substituted aryl C₁₋₆ alkyl, heterocyclic C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, substituted heteroaryl C₁₋₆ alkyl, or substituted heterocyclic C₁₋₆ alkyl;

15 with the proviso that

(a) at least one of X, Y and Z must contain a heteroatom;

(b) when Y is -CH₂-, then only one of X and Z can be a heteroatom;

(c) when Y is -CO- and both X and Z are heteroatoms, then one must be -NH- and the other -NH- or -O-;

(d) when A¹ is alkyl, X is -O- or -S-, Y is CHR⁹ and Z is a chemical bond, then A³ cannot be H or C₁₋₆ alkyl;

(e) when A¹ is alkyl, X is a chemical bond, Y is CHR⁹ and Z is -O- or -S-, then A³ cannot be C₁₋₆ alkyl;

25 (f) when A¹ is a chemical bond, X is O or S, Y is CH₂, and Z is a chemical bond, then A³ cannot be aryl or aryl C₁₋₆ alkyl;

(g) when A¹ is a chemical bond, X is a chemical bond, Y is CO, and Z is O, then A³ cannot be H, alkyl, aryl, aryloxyalkyl, alkanoyloxyalkyl or aroyloxyalkyl; or

30 (h) when A¹ is a chemical bond, X is a NH, Y is CH₂, and Z is a chemical bond, then A³ cannot be alkyl, aryl, arylalkyl, cycloalkyl, or cycloalkyl alkyl;

R¹ is HN(OH)CO-, HCON(OH)-, CH₃CON(OH)-, HO₂C-, HS-, or phosphinate;

35 R² is OR⁶ or NR¹⁰R⁶

where R⁶ is hydrogen, C₆₋₁₂ aryl, or (CH₂)_nR⁷,

wherein R⁷ is

hydrogen, phenyl, substituted phenyl, hydroxy, C₁-6
alkoxy, C₂-7 acyloxy, C₁-6 alkylthio, phenylthio,
sulfoxide of a thio, sulfone of a thio, carboxyl, (C₁-6
5 alkyl) carbonyl, (C₁-6 alkoxy) carbonyl, (C₁-6
alkyl)aminocarbonyl, arylaminocarbonyl, amino, substi-
tuted acyclic amino, heterocyclic amino, N-oxide of an
amine, or C₂-7 acylamino, and n is 1 to 6; or

R³ and R⁶ taken together are a group of the formula -(CH₂)_m-

10 where m is from 5 to 12, optionally interrupted by a NR⁸
group

where R⁸ is selected from hydrogen, C₁-6 alkyl, C₁-6
alkylcarbonyl, C₁-6 alkoxycarbonyl, aryl, aralkyl,
or aralkyloxycarbonyl, in each of which the aryl
15 moiety is optionally substituted;

R³ is a characterizing group of an alpha amino acid, C₁-6 alkyl,
aryl methylene, substituted aryl methylene, C₃-10 cycloalkyl,
C₃-10 cycloalkyl methylene, aryl, substituted aryl, fused
20 bicycloaryl methylene, fused substituted bicycloaryl methylene,
conjugated bicycloaryl methylene, or conjugated substituted
bicycloaryl methylene;

R⁴ is hydrogen or C₁-4 alkyl;

R⁵ is hydrogen, phenyl, substituted phenyl, amino, hydroxy,
mercapto, C₁-4 alkoxy, C₁-6 alkylamino, C₁-6 alkylthio, C₁-6
25 alkyl or C₂-6 alkenyl,

optionally substituted by

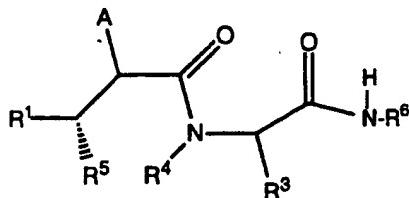
30 alkyl, phenyl, substituted phenyl, heterocyclic,
substituted heterocyclic, amino, acylated amino,
protected amino, hydroxy, protected hydroxy, mercapto,
protected mercapto, carboxy, protected carboxy, or
amidated carboxy;

R⁹ is hydrogen or C₁-4 alkyl;

R¹⁰ is hydrogen or C₁-4 alkyl;

and the salts, solvates and hydrates thereof.

Preferred compounds have the structure:



wherein

5 A is A¹- A²- A³

wherein

A¹ is (CH₂)_n, and n is 3 - 5,

A² is X-Y-Z,

wherein,

10 X is a chemical bond or -NH-;

Y is -(C=O)-, -CH₂-, -(CHCH₃)-,

Z is -O-, -NH-, or a chemical bond; and

A³ is

15 hydrogen, methyl, ethyl, propyl, butyl, pentyl, phenyl, methylphenyl, chlorophenyl, methoxyphenyl, phenylmethylen, methoxyphenylmethylen, methylphenylmethylen or phenylethylen;

R¹ is HO₂C- or HN(OH);

20 R³ is

tertiary butyl, phenylmethylen, cyclohexyl methylen, or 3,5 dimethyl phenylmethylen;

R⁴ is hydrogen or methyl;

R⁵ is hydrogen, methyl, 2-methylpropyl, or 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl; and

R⁶ is

methyl,

2-pyridylethylen,

phenylethylen,

30 4-sulfamoyl phenylethylen, or morpholino-N-ethylene;

Even more preferred are compounds wherein A is

- (CH₂)₄-O-H,
- (CH₂)₃-C=O-O-H,
- (CH₂)₃-C=O-NH-(CH₂)₂CH₃,
- 5 - (CH₂)₃-C=O-NH-(CH₂)₂-phenyl
- (CH₂)₃-CH(CH₃)-O-H,
- (CH₂)₄-NH-C=O-(CH₂)₂CH₃,
- (CH₂)₄-O-phenyl,
- (CH₂)₄-O-(4-chlorophenyl),
- 10 - (CH₂)₄-O-(3-methylphenyl),
- (CH₂)₄-O-(4-methoxyphenyl),
- (CH₂)₄-O-(4-methylphenyl),
- (CH₂)₅-O-phenyl,
- (CH₂)₄-O-CH₂-phenyl,
- 15 - (CH₂)₅-O-CH₂-(4-methylphenyl), or
- (CH₂)₃-O-CH₂-(4-methylphenyl).

Included in the invention are pharmaceutical compositions comprising an effective amount of at least one of the compounds 20 and methods of promoting an antiarthritic effect in a mammal in need thereof comprising administering thereto a matrix metalloproteinase inhibitory amount of at least one compound of the invention.

25

DETAILED DESCRIPTION OF THE INVENTION

Hereafter in this specification the term "compound" includes salt solvates and hydrates unless the context requires otherwise.

30

As used herein the term "C₁-6 alkyl" refers to a straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl and the like.

35

The term "C₂-6 alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbons and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include, for example, vinyl, 1-propenyl, 1- and 2-
5 butenyl, 2-methyl-2-propenyl etc.

The term "cycloalkyl" refers to a saturated alicyclic moiety having from 3 to 8 carbon atoms and includes for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

10 The term "heterocyclic" refers to a saturated or unsaturated ring containing at least one hetero atom such as nitrogen, oxygen or sulphur and includes for example, furan, pyrrole, thiophen, morpholine, pyridine, dioxane, imidazoline, pyrimidine, pyridazine
15 and the like.

20 The term "substituted", as applied to a phenyl or other aromatic ring, means substituted with up to four substituents each of which independently may be C₁-6 alkyl, C₁-6 alkoxy, hydroxy, thiol, C₁-6 alkylthiol, amino, substituted amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, -CONH₂ or -CONH^A, wherein R^A represents a C₁-6 alkyl group or an amino acid such as alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine,
25 tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine or histidine.

30 The term "amino acid" means one of the following R or S alpha-amino acids: glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid and aspartic acid.

Derivatives of amino acids include acid halides, esters and
35 substituted or unsubstituted amides, for example N-methyl amide.

There are several chiral centers in the compounds according to the invention because of the presence of asymmetric carbon atoms.

The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with the appropriate R or S stereochemistry at each chiral center. The invention is understood to include all such diastereomers and mixtures thereof.

Preferred compounds include the following:

10

- a/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-5-(carboxy)pentanoyl]-L-phenylalanine N-methylamide;
- b/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;
- c/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(propylamino)-6-(oxo)hexanoyl]-L-phenylalanine N-methylamide;
- d/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-(6RS)-6-(hydroxy)heptanoyl]-L-phenylalanine N-methylamide;
- e/ (2S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(hydroxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
- f/ (2S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
- g/ N-[(2'R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(4'-oxobutylamino)hexanoyl]-L-phenylalanine N-methylamide;
- h/ 2(S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
- i/ N-[(2R)-2-[(1'S)-1'-(Methyl)-2'-(hydroxyamino)-2'-(oxo)-ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;
- j/ N-[(2R)-2-[(1'S)-1'-(Methyl)-2'-(hydroxyamino)-2'-(oxo)-ethyl]-6-(oxo)-6-(propylamino)hexanoyl]-L-phenylalanine N-methylamide;

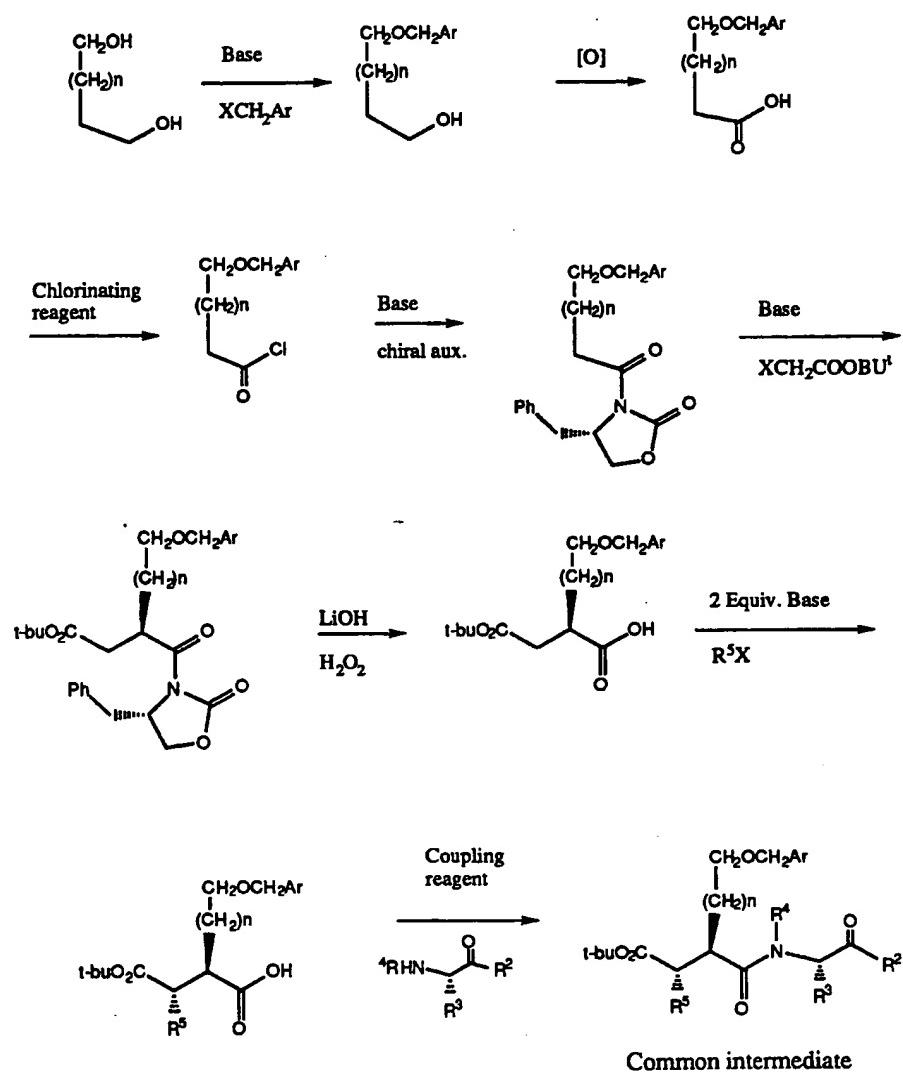
- k/ (2S)-N-2-[(2'R)-[(1"R)-1"- (1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl-2"- (hydroxyamino)-2"- (oxo)ethyl]-6'- (phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
- 5 l/ N-[(2R)-2-[2'- (Hydroxyamino)-2'- (oxo)ethyl]-6- (oxo)-6- (propylamino)hexanoyl]-L-phenylalanine N-2-phenylethylamide;
- m/ (2S)-N-2-[(2'R)-2'-[(1"S)-1"- (Methyl)-2"- (hydroxyamino)-2"- (oxo)ethyl]-6- (phenylmethoxy)hexanoyl]amino-3,3-
- 10 10 dimethylbutanoic acid N-2-phenylethylamide;
- n/ (2S)-N-2-[(2'R)-2'-[(1"S)-1"- (Methyl)-2"- (hydroxyamino)-2"- (oxo)ethyl]-6'- (oxo)-6'- (propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;
- 15 o/ (2S)-N-2-[(2'R)-2'-[(1"S)-1"- (Methyl)-2"- (hydroxyamino)-2"- (oxo)ethyl]-6'- (oxo)-6'- (propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;
- p/ (2S)-N-[(2'R)-2'-[2"- (Hydroxyamino)-2"- (oxo)ethyl]-6'- (phenylmethoxy)hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4'-sulfamoyl)phenylethylamide;
- 20 q/ N-[(2R)-2-[2'- (Hydroxyamino)-2'- (oxo)ethyl]-6'- (phenylmethoxy)hexanoyl]-L-(3,5-dimethyl)phenylalanine N-2-(4'-sulfamoyl)phenylethylamide;
- r/ (2S)-N-2'-[(2'R)-2'-[2"- (hydroxyamino)-2"- (oxo)ethyl]-6'- [(4-methoxy)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;
- 25 s/ (2S)-N-2'-[(2'R)-2'-[2"- (hydroxyamino)-2"- (oxo)ethyl]-6'- [(4-methyl)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;
- t/ (2S)-N-2'-[(2'R)-2'-[2"- (Hydroxyamino)-2"- (oxo)ethyl]-6'- [(1-oxo)butylamino]hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4'-sulfamoyl)phenylethylamide;
- 30 u/ (2S)-N-2-[(2'R)-2'-[(1"S)-1"- (Methyl)-2"- (hydroxyamino)-2"- (oxo)ethyl]-6- (phenylmethoxy)hexanoyl]amino-3,3-
- 35 dimethylbutanoic acid N-methylamide;
- v/ (2S)-N-2-[(2'R)-2'-[(1"S)-1"- (2-Methylpropyl)-2"- (hy-

- droxyamino)-2"--(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-
amino-3,3-dimethylbutanoic acid N-methylamide;
- w/ N-[(2R)-2-[2'--(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenoxy)-
hexanoyl]-L-phenylalanine N-methylamide;
- 5 x/ N-[(2R)-2-[2'--(Hydroxyamino)-2'-(oxo)ethyl]-7-(phenoxy)-
heptanoyl]-L-phenylalanine N-methylamide;
- y/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid
N-2-phenylethylamide;
- 10 z/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid
N-2-(4'-sulfamoyl)phenylethylamide;
- aa/ N-[(2R)-2-[2'--(Hydroxyamino)-2'-(oxo)ethyl]-5-(phenyl-
methoxy)pentanoyl]-L-phenylalanine N-methylamide;
- 15 ab/ N-[(2R)-2-[2'--(Hydroxyamino)-2'-(oxo)ethyl]-7-(phenyl-
methoxy)heptanoyl]-L-phenylalanine N-methylamide;
- ac/ N-[(2R)-2-[2'--(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenyl-
oxy)hexanoyl]-L-phenylalanine N-methylamide;
- ad/ N-[(2R)-2-[2'--(Hydroxyamino)-2'-(oxo)ethyl]-7-[(phenyl-
oxy)heptanoyl]-L-phenylalanine N-methylamide;
- 20 ae/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(2-phenethylamino)-6'(oxo)hexanoyl]amino-3,3-
dimethylbutanoic acid N-methylamide;
- af/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(4-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic
acid N-methylamide;
- 25 ag/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(4-chlorophenoxy)hexanoyl]amino-3,3-dimethylbutanoic
acid N-methylamide;
- 30 ah/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(3-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic
acid N-methylamide; and
- ai/ (2S)-N-2'-[(2'R)-2'-(carboxymethyl)-6'-(3-
methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-
methylamide.

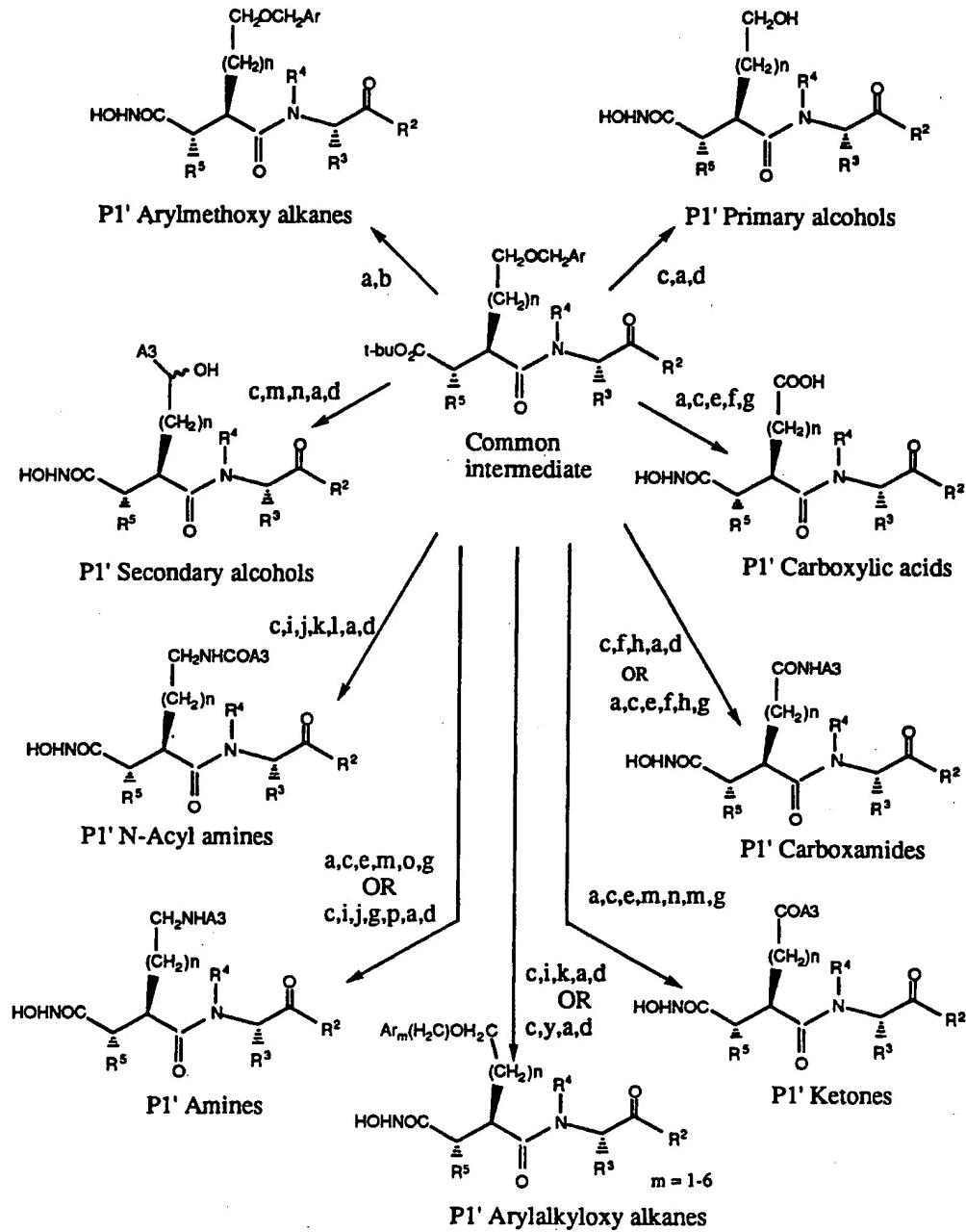
Compounds of the invention may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

- 5 According to another aspect of the invention, there is provided a process for preparing compounds of the invention as defined above. The following is a schematic for the preparation of a common intermediate used to prepare compounds of the invention by various routes.

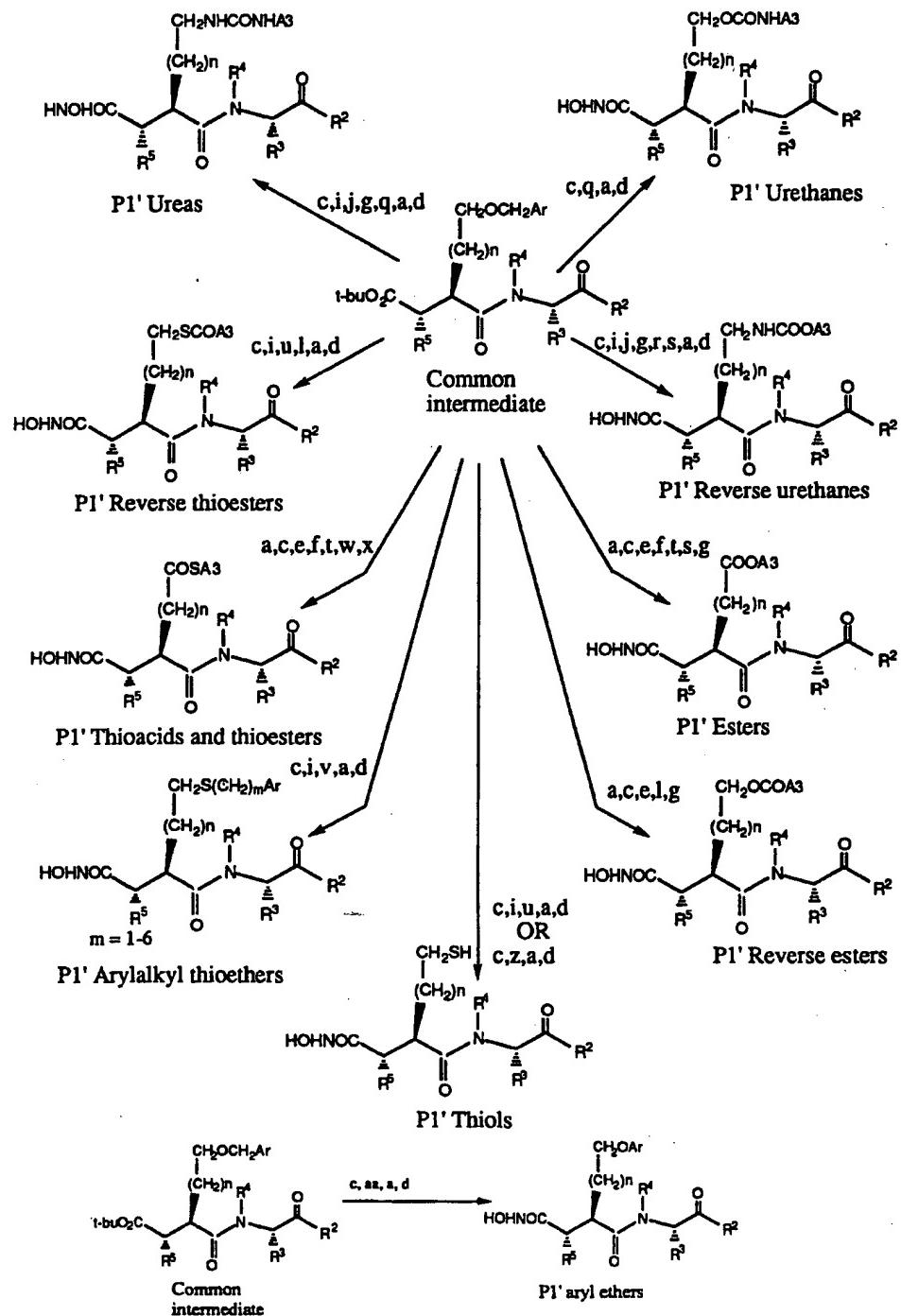
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Synthesis of compounds of the invention from the common intermediate



Synthesis of other compounds of the invention from the common intermediate.



- a) TFA
- b) i) Isobutylchloroformate, NMM, TMSONH₂, H₂O
- c) Hydrogenolysis
- d) i) Isobutylchloroformate, NMM, TMSONH₂ ii) H₂O OR
5 i) isobutylchloroformate, NMM, BzONH₂ ii) 5% Pd-C, H₂
- e) Isobutylchloroformate, NMM, BzONH₂
- f) Oxidation
- g) Cat. H₂
- h) Coupling with A₃NH₂, where A₃ is not H
- 10 i) MsCl
- j) NaN₃
- k) Ar(CH₂)_mO⁻
- l) Coupling with A₃COCl, where A₃ is not H
- m) PDC, CH₂Cl₂
- 15 n) CH₃Ti(OCHMe₂)₃ OR A₃Mgx, where A₃ is not H
- o) Reductive amination with NH₄OAc (Primary amine) or A₃NH₂
(Secondary amine), where A₃ is not H
- p) Reductive amination with A₃CHO or alkylation with A₃X, where
A₃ is not H
- 20 q) A₃NCO, where A₃ is not H
- r) COCl₂ or Triphosgene
- s) A₃O_H, where A₃ is not H
- t) (COCl)₂
- u) NaSH
- 25 v) Ar(CH₂)_mS⁻
- w) A₃S
- x) Cat. H₂, with repeated additions of catalyst
- y) Base, Ar(CH₂)_mX
- z) i) PPh₃, i-proOCN=NCO-i-pro, CH₃COSH ii) LiOH
- 30 aa) PPh₃, DEAD, ArOH

In a further aspect of the invention there is provided the use of a compound of invention in medicine, particularly in a method of treatment of diseases in which collagenolytic activity is
35 important.

In another aspect of the invention there is provided the use of a compound of the invention in the preparation of an agent for the treatment of diseases in which collagenolytic activity is
40 important.

The invention also provides a pharmaceutical composition comprising one or more compounds of the invention in association with one or more non-toxic pharmaceutically acceptable carriers

and/or diluents and/or adjuvants. Other active ingredients may also be included in the compositions of the invention.

5 The compositions of the present invention may be formulated for administration by any route depending on the disease being treated. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions:

- 10 Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients. Examples of these are binding agents such as syrup, acacia, gelatin, sorbitol, tragacanth, and polyvinylpyrrolidone; fillers 15 for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example, magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods 20 well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain 25 conventional additives such as suspending agents for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, 30 fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavoring or coloring agents.
- 35 The dosage unit involved in oral administration may contain from about 1 to 250 mg, preferably from about 25 to 250 mg. A suitable

daily dose for a mammal may vary widely depending on the condition of the patient. However, a dose of about 0.1 to 300 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight may be appropriate.

5

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of 10 pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers such as sodium 15 metabisulphite; preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hydrocellulose may also be included.

20 The dosage employed for the topical administration will, of course, depend on the size of the area being treated.

The active ingredient may also be administered parenterally in a sterile medium. The drug depending on the vehicle and 25 concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetic, preservatives and buffering agents can be dissolved in the vehicle.

30 For use in the treatment of rheumatoid arthritis, the compounds of this invention can be administered by the oral route or by injection intra-articularly into the affected joint. The daily dosage for a 70 kg mammal will be in the range of 1 mgs to 1 gram.

35 The following examples illustrate the invention, but are not intended to limit the scope in any way.

EXAMPLE 1

PREPARATION OF INTERMEDIATES

- 5 1a. Synthesis of 6-Phenylmethoxyhexane-1-ol. Hexane-1,6-diol [25 g, 0.21 mol] is dissolved in dry/distilled THF (300 mL) under a N₂ atmosphere. 80% NaH [6.3 g, 0.21 mol] is then added with vigorous stirring in small portions over ~10-20 minutes Evolution of gas (H₂) is noted. The reaction is
10 heated to reflux with continued vigorous stirring for 4.5 hours resulting in the formation of a thick gray-colored solid. Benzyl bromide [25 mL, 0.21 mol] is added in one portion, and the reaction is allowed to reflux for ~22 hours. The solid mass is replaced by a white-colored solid (NaBr)
15 which is filtered from the reaction after cooling to room temperature. The solid is washed with THF and the combined filtrates are evaporated, leaving a yellow oil. The oil is taken up in Et₂O, and washed successively with distilled water until there is no indication of the starting diol (as determined by TLC) and then washed with brine. The organic layer is dried over Na₂SO₄ and the Et₂O is evaporated. The resulting oil is a mixture of the di-and mono-benzylated hexanol (approximately a 2:1 ratio of mono to di-benzylated based on ¹H- NMR data, 38.05 g, 60% yield). The mixture is
20 used without further purification in the next step. Isolation of a small amount of mono benzylated product gives the following data; ¹H- NMR (CDCl₃): δ 1.3-1.7 (m, 9H, -(CH₂)₄ and -OH), 3.5 (t, 2H, -CH₂OCH₂Ph), 3.64 (t, 2H, -CH₂OH), 4.5 (s, 2H, -OCH₂Ph), 7.3 (m, 5H, Ar).
25
- 30 1b. Synthesis of 6-Phenylmethoxyhexanoic acid A solution of compound obtained in example 1a (38 g, 0.114 mol) in 50 mL of dry DMF is added dropwise to a solution of DMF (300 mL) containing pyridinium dichromate (128 g, 0.342 mol) The reaction is slightly exothermic and so is maintained at 10-20°C for the first few hours of the reaction. The reaction

is stirred for 9 hours at room temperature. The reaction is diluted with 2.5 L H₂O and extracted 10 times with EtOAc (150 mL) which is in turn washed with H₂O. Remaining PDC is removed by filtering the EtOAc extractions through anhydrous MgSO₄. The organic layer is then extracted with 1 N NaOH (5 times). The combined basic extractions are washed with several portions of fresh EtOAc. The basic layer is then slowly acidified with concentrated HCl to a pH 2-3 and extracted 5 times with EtOAc. The combined organic layers are dried over Na₂SO₄ and the solvent is evaporated to afford pure acid (~75% yield).

15 ¹H- NMR (CDCl₃): δ 1.45 (m, 2H, -CH₂), 1.65 (m, 4H, -(CH₂)₂), 2.35 (t, 2H, -CH₂COOH), 3.37 (t, 3H, -CH₂OCH₂Ph), 4.5 (s, 2H, -OCH₂Ph), 7.3 (m, 5H, Ar).

1c. Synthesis of 6-phenylmethoxyhexanoyl chloride 30.52 g of the compound of Example 1b [0.14 mol] is dissolved in dry CH₂Cl₂ and cooled to 0°C. Oxalyl chloride [13.09 mL, 0.154 mol] is added in one portion. Some minor gas evolution (CO₂) is observed. ~5 drops of dry DMF is added with stirring and the gas evolution is noticeably more vigorous. The reaction is allowed to stir while warming to room temperature until no more bubbling is observed and then stirred ~30 minutes more. The solvent and remaining oxalyl chloride is removed under vacuum. A yellow oil with some solid dispersed in it remains. The oil is filtered through a dry filter, then is placed on high vacuum suction until used in the next step (29.6 g, 90+% yield).

30 ¹H- NMR (CDCl₃): δ 1.37 (m, 2H, -CH₂), 1.7 (m, 4H, -(CH₂)₂), 2.9 (t, 2H, -CH₂COCl), 3.5 (t, 2H, -CH₂OCH₂Ph), 4.5 (s, 2H, -OCH₂Ph), 7.35 (m, 5H, Ar).

1d. Synthesis of (4S)-4-benzyl-3-[(6'-phenylmethoxy)hexanoyl]-2-oxazolidinone (S)-(--)-4-benzyl-2-oxazolidinone [21.08 g, 0.12 mol] is dissolved in dry/distilled THF (250 mL) under a N₂ atmosphere and cooled to -78°C. A solution of 1.6M n-butyl lithium in hexane (n-BuLi) [74.77 mL, 0.12 mol] is added dropwise with stirring while maintaining the reaction between -65°C to -78°C. Near the end of this addition, the reaction is observed to turn a deeper yellow color, indicating benzylic protons being deprotonated and that enough n-BuLi has been added. The reaction is allowed to stir at -78°C for 25 minutes, then 28.8 g of the compound of example 1c [0.12 mol] in THF (100 mL) is added dropwise, maintaining the reaction near -78°C. The deep yellow color of the reaction lightens with the addition. The reaction is allowed to gradually warm to room temperature and then is quenched with the addition of a saturated solution of NH₄Cl (150 mL). The THF is evaporated and the residue is extracted into Et₂O which is washed with 0.5 N NaOH (5 times), H₂O, and finally brine. It is then dried over Na₂SO₄ and evaporated to an oil residue which is purified by flash column chromatography to give 46.5 g (85% yield).

¹H-NMR (CDCl₃): δ 1.5 (m, 2H, -CH₂), 1.7 (m, 4H, -CH₂)₂, 2.77 (dd, 1H, -CHCH₂Ph), 2.95 (m, 2H, -CH₂CON), 3.3 (dd, 1H, -CHCH₂Ph), 3.5 (t, 2H, -CH₂OCH₂Ph), 4.17 (m, 2H, ring -CH₂), 4.5 (s, 2H, -OCH₂Ph), 4.67 (m, 1H, ring -CH), 7.3 (m, 10H, Ar).

1e. Synthesis of (4S)-4-benzyl-3-[(2'R)-2'-(tert-butoxy-carbonylmethyl)-6'-(phenylmethoxy)hexanoyl]-2-oxazolidinone Diisopropylamine [1.82 mL, 13 mmol] in dry/distilled THF (10 mL) is cooled to -15°C under a N₂ atmosphere. A solution of 1.6M n-BuLi in hexane [8.12 mL, 13 mmol] is slowly added dropwise with stirring while maintaining the temperature below 0°C. The reaction is allowed to stir at

0°C for 30 minutes and then cooled to -78°C. The product of example 1d [4.71 g, 12 mmol] in 50 mL THF is added dropwise with stirring while maintaining the temperature near -78°C. Stirring is continued for 30 minutes. A solution of t-butyl bromoacetate [1.8 mL, 12 mmol] in THF (25 mL) is then added dropwise at -78°C. Following addition, the reaction is allowed to warm to room temperature and then quenched cautiously with H₂O. The THF is evaporated and the residue extracted into EtOAc. The organic layer is washed with 5% NaHCO₃, 5% citric acid, and brine, and then dried over Na₂SO₄. The solvent is evaporated, and the resulting oil solidified on standing. The solid product is recrystallized with EtOAc/hexane several times, or alternatively, flash chromatography is used. This affords 3.21 g of a white fluffy crystal (55% yield).

¹H-NMR (CDCl₃): δ 1.4-1.72 (s and m, 15H, t-butyl and -(CH₂)₃), 2.48 (dd, 1H, -COCH₂CHCO), 2.75 (overlapping dd, 2H, one -COCH₂CHCO and one -CHCH₂Ph), 3.34 (dd, 1H, -CHCH₂Ph), 3.45 (t, 2H, -CH₂OCH₂Ph), 4.15 (m, 3H, ring -CH₂ and -CH₂CHCO), 4.48 (s, 2H, -OCH₂Ph), 4.63 (m, 1H, ring -CH), 7.3 (m, 10H, Ar).

1f. Synthesis of (2R)-2-(tert-butoxycarbonylmethyl)-6-(phenylmethoxy) hexanoic acid 0.5 g of the compound of Example 1e is dissolved in 15 mL of a 4:1 THF/H₂O solution and cooled to about 0°C, but not below, under a N₂ atmosphere. Slowly, dropwise and with stirring, 30% aqueous H₂O₂ [0.5 mL, 4.4 mmol] is added. After stirring 5 minutes, a solution of LiOH·H₂O [0.07 g, 1.5 mmol] in 2 mL H₂O is added dropwise. Some gas evolution is observed. The reaction is warmed slowly to room temperature and stirred for 1 hour, then a solution of Na₂SO₃ [0.2 g, 1.7 mmol] in 2 mL H₂O is added dropwise. Some heat is evolved during this process, so the reaction is cooled with an ice bath. After

stirring ~20 minutes the THF is evaporated (below 30°C) and the basic, aqueous mixture remaining is extracted with EtOAc (5 times). These combined extracts contain the free benzyl oxazolidinone which can be recrystallized and recycled for further use.

The basic layer is then cooled and acidified with the slow addition of concentrated HCl to a pH 2-3. The cloudy mixture is then extracted 5 times with EtOAc, dried over Na₂SO₄ and evaporated to give 0.29 g of pure acid (86% yield).

¹H-NMR (CDCl₃): δ 1.42-1.7 (s and m, 15H, 5-butyl and -(CH₂)₃), 2.37 (dd, 1H, -COCH₂CHCO), 2.6 (dd, 1H, -COCH₂CHCO), 2.8 (m, 1H, -COCH₂CHCO), 3.45 (t, 2H, -CH₂OCH₂Ph), 4.5 (s, 2H, -OCH₂Ph), 7.3 (m, 5H, Ar).

1g. Synthesis of N-[2R]-2-(tert-butoxycarbonylmethyl)-6-(phenylmethoxy) hexanoyl-L-phenylalanine N-methylamide A solution of the product of Example 1f (3.36 g, 0.01 mol) and L-phenylalanine N-methylamide TFA salt (2.9 g, 0.01 mol) in dry dimethylformamide (40 mL) under nitrogen are cooled to -6°C and treated dropwise with diethylcyanophosphonate (1.63 g, 0.01 mol) followed by triethylamine (3.03 g, 0.03 mol). The reaction mixture is stirred at 0°C for 1 hour, warmed to room temperature over 1 hour, and then stirred for two additional hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The combined ethyl acetate layers are sequentially washed with 5% citric acid, saturated sodium bicarbonate, water, and brine. The ethyl acetate is separated, dried (Na₂SO₄), and evaporated. The residue is purified by silica gel column chromatography using 50-70% ethyl acetate in hexanes as the eluent. The appropriate fraction yielded 4.21 g of the product (85%).

5 ¹H NMR (CDCl₃) δ 1.20 -180 (m, 15H, CCH₂CH₂CH₂C and t-butyl H), 2.25 - 2.60 (m, 3H, CH₂CO and CHCO), 2.65 (d, 3H, NCH₃), 3.38 (t, 2H, CCH₂O), 3.07 (d, 2H, ArCH₂C), 4.44 (s, 2H, OCH₂Ar), 4.57 (q, 1H, NCH), 6.34 (q, 1H, NH), 6.52 (d, 1H, NH), 7.20 - 7.60 (m, 10H, ArH).

EXAMPLE 2

10 N-[2R]-2-[2'-(Hydroxyamino)-2'(oxo)ethyl]-6-(phenylmethoxy)hexanoyl-L-phenylalanine N-methylamide

2a. Synthesis of N-[2R]-2-(carboxymethyl)-6-(phenylmethoxy)hexanoyl-L-phenylalanine N-methylamide A solution of the compound formed in Example 15 1g (0.33 g, 0.66 mmol) in trifluoroacetic acid (7 mL) and water (3 mL) is stirred at room temperature for 6 hours. The solvents are removed on a rotary evaporator. The residue is treated with acetonitrile and evaporated (three times) in order to azeotrope water. The crude product is placed on a 20 high vacuum pump for 2 hours to give a gummy material, which is triturated with diethyl ether to produce a colorless solid. The solid was collected by filtration and air dried. (0.227 g, 78% yield).

25 ¹H NMR(MeOH-d₄) δ 0.80 - 1.50 (m, 6H, CCH₂CH₂CH₂C), 2.00 - 2.60 (m, 6H, NCH₃, CH₂CO and CHCO), 2.74 (dd) and 2.92 (dd), (2H, CCH₂Ar), 3.20 (t, 2H, OCH₂C), 4.25 (m, OCH₂Ar and NCH), 6.90 - 7.30 (m, 10H, ArH).

30 2b. Under nitrogen atmosphere, the carboxylic acid formed in Example 2a (0.44 g, 1.0 mmol) is dissolved in dry tetrahydrofuran (20 mL), and treated with N-methyl morpholine (0.13 g, 1.15 mmol) via syringe. The reaction mixture is cooled to -10°C and treated with isobutylchloroformate (0.15 35 mL, 1.15 mmol) via syringe. After stirring the suspension

for 20 minutes, O-(trimethylsilyl)hydroxylamine (0.12 mL, 1.15 mmol) is added via syringe and the reaction mixture is stirred in the cold for 3 hours. The ice bath is removed, the reaction mixture is filtered, and the filtrate is
5 evaporated to a colorless solid. The solid is triturated with methylene chloride, collected by filtration, and air dried to give 0.27 g of a colorless solid (59% yield).

10 ^1H NMR(MeOH-d₄) δ 1.6-1.1 (m, 6H, CCH₂CH₂CH₂C), 2.22 (dd, 1H) and 2.10 (dd, 1H) CH₂CON, 2.60 (m, 1H, CH₂CHCO), 2.64 (d, 3H, NHCH₃), 3.15 (dd, 1H) and 2.96 (dd, 1H, OCH₂Ar), 3.40 (t, 2H, CH₂OCH₂Ar), 4.46 (s, 2H, ArCH₂O), 4.49 (M, 1H, NCHCO), 7.35-7.10 (m, 10H), 7.90 (m, 1H), 8.20 (d, 1H).

15

EXAMPLE 3

N-[*(2R*)-2-[2'-(hydroxyamino)-2'-(oxo)ethyl]-6-(hydroxy)hexanoyl-L-phenylalanine N-methylamide

20 3a. Synthesis of N-[*(2R*)-2-(tert-butoxycarbonylmethyl)-6-(hydroxy)hexanoyl-L-phenylalanine N-methylamide Under nitrogen atmosphere, a solution of the compound formed in Example 1g (2.5 g, 0.005 mol) in methanol (50 mL) is treated with ammonium formate (2.5 g) and 10% Pd/C (1.0 g). The
25 mixture is heated to reflux for 4 hours at which point 2.5 g of ammonium formate is added and refluxing is continued for 2 hours. The heat is removed and the reaction mixture is allowed to stand overnight at room temperature. After 15 hours, ammonium formate (2.5 g) and 10% Pd/C (0.2 g) are added
30 and the reaction mixture is heated at reflux for 4 hours. The reaction mixture is cooled and the catalyst is collected via filtration. The filtrate is evaporated to dryness and the residue is partitioned between water and ethyl acetate. The ethyl acetate layer is washed with water, then dried (Na₂SO₄), filtered, and evaporated. The product is purified
35

by silica gel column chromatography using 5% methanol in ethyl acetate as the eluent, (1.3 g, 64% yield).

5 ¹H NMR (CDCl₃) δ 1.00 - 1.70 (m, 15H, CCH₂CH₂CH₂C and t-butyl H), 2.25 - 2.60 (m, 3H), 2.69 (d, 3H, NCH₃), 3.00 - 3.20 (m, 2H, CH₂Ar), 3.50 - 3.70 (m, 2H, CH₂O), 4.56 (q, 1H, NCH), 6.15 (m, 1H, NH), 7.13 (d, 1H, NH), 7.15 - 7.45 (m, 5H, ArH).

10 3b. Synthesis of N-[*(2R*)-2-(Carboxymethyl)-6-(hydroxy)-hexanoyl-L-phenylalanine N-methylamide The product formed in Example 3a (0.7 g, 1.72 mmol) is dissolved in 10 mL of a 7:3 trifluoroacetic acid-water mixture and stirred at room temperature for 4.5 hours. The solvents are removed on a rotary evaporator and the residue is treated with acetonitrile and evaporated (three times) in order to azeotrope water. The colorless solid is dried on a high vacuum pump for 4 hours, then triturated with diethyl ether. The colorless solid is collected by filtration and dried. (0.6 g, 100% yield).

20 25 ¹H NMR (MeOH-d₄) δ 0.88 - 1.60 (m, 6H, CCH₂CH₂CH₂C), 2.15-2.60 (m, 6H, NCH₃, CH₂CO and CHCO), 2.75 (dd) and 2.90 (dd) (2H, CH₂Ar), 4.10 (t, 2H, CH₂O), 4.30 (q, 1H, NCH), 6.90-7.30 (m, 5H, ArH), 7.58 (m, 1H, NH), 8.00 (d, 1H, NH).

25 3c. Under nitrogen atmosphere, the product of example 3b (0.245 g, 0.7 mmol) is dissolved in dry tetrahydrofuran (20 mL), cooled to -15°C and treated with N-methylmorpholine (0.14 g, 1.33 mmol). After 5 minutes, isobutylchloroformate (0.18 g, 1.33 mmol) is added dropwise and the reaction mixture is stirred for 15 minutes. O-(trimethylsilyl)hydroxylamine (0.42 g, 3.9 mmol) is added dropwise. The reaction mixture is stirred at -15°C for 1 hour, followed by 1 hour at 0°C, then 30 minutes at room temperature. The reaction mixture is filtered and the filtrate is evaporated to dryness. The

residue is triturated first with diethyl ether followed by methylene chloride. The solid is collected by filtration and purified by preparative thin-layer chromatography using 15% methanol in methylene chloride as eluent, giving a colorless solid. (0.12 g, 25% yield).

5

¹H NMR(MeOH-d₄) δ 0.80 -1.50 (m, 6H, CCH₂CH₂CH₂C), 1.80 - 2.10

(m, 2H, CH₂CO), 2.30 - 2.44 (m, 1H, CHCO), 2.47 (s, 3H,

NCH₃), 2.95 (dd) and 2.72 (dd) (2H, ArH), 3.25 (t, 2H, CH₂O),

4.30 (q, 1H, NCH), 6.90 - 7.30 (m, 5H, ArH).

10 Mass (FAB): 366 (MH⁺)

EXAMPLE 4

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N-[2R]-2-[2'-(Hydroxymino)-2'-(oxo)ethyl]-5-
(carboxy)pentanoyl-L-phenylalanine N-methylamide

20

4a. Synthesis of N-[2R]-2-[2'-(Phenylmethoxyamino)-2'-(oxo)ethyl]-6-(hydroxy)hexanoyl-L-phenylalanine N-methylamide

Under nitrogen atmosphere, the carboxylic acid product formed in Example 3b (0.035 g, 0.1 mmol) is dissolved in anhydrous dimethylformamide (1 mL) and treated with N-methylmorpholine (0.017 mL, 0.15 mmol). The reaction is cooled to -10°C and treated dropwise with isobutylchloroformate (0.02 mL, 0.15 mmol). The reaction is stirred for 20 minutes, then a suspension of O-benzylhydroxylamine hydrochloride (0.024 g, 0.15 mmol) and N-methylmorpholine (0.017 mL, 0.15 mmol) in dimethylformamide (1.5 mL) is added. After stirring 20 minutes, the ice bath is removed and the reaction mixture is stirred for 3 hours. The dimethylformamide is removed on a rotary evaporator and the residue is dissolved in ethyl acetate. The ethyl acetate is washed with 5% citric acid and 5% sodium bicarbonate, then dried (Na₂SO₄), filtered, and evaporated. The solid is triturated with diethyl ether and collected by filtration to give 10 mg (2% yield) of compound.

5 ¹H NMR (MeOH-d4) δ 1.6-1.1 (m, 6H, CCH₂CH₂CH₂C), 2.13 (m, 2H,
CH₂CHCO), 2.67 (m, 1H, CH₂CHCO), 2.69 (d, 3H, NCH₃), 3.15
(dd) and 2.94 (dd), (2H, CH₂Ar), 3.48 (t, 2H, CH₂OH), 4.50
10 (m, 1H, NCHCO), 4.80 (s, 2H, ArCH₂O), 7.4-7.17 (m, 10H, Ar),
7.94 (m, 1H, NH), 8.24 (d, 1H, NH).

- 15 4b. Synthesis of N-[L(2R)-2-[2'-(Phenylmethoxyamino)-2'-
oxoethyl]-5-(carboxy)pentanoyl-L-phenylalanine N-methylamide A solution of the compound of Example 4a (0.05
g, 0.11 mmol) in dimethylformamide (1 mL) is treated with
pyridinium dichromate (0.144 g, 0.38 mmol) at room
temperature overnight. The reaction mixture is partitioned
between ethyl acetate and water. The aqueous layer is
separated and extracted with ethyl acetate. The ethyl
acetate extracts are combined, dried (Na₂SO₄), filtered, and
evaporated to a gum. Trituration with diethyl ether produces
an off-white solid (0.023 g, 45% yield).
- 20 25 1H NMR (MeOH-d4) δ 1.6-1.1 (m, 6H, CCH₂CH₂CH₂C), 2.27-2.02 (m,
4H, CH₂CHCO and CH₂COOH), 2.70 (m, 4H, NCH₃ and CH₂CHCO),
3.15 (dd) and 2.92 (dd), (2H, CH₂Ar), 4.55 (m, 1H, NCHCO),
4.80 (s, 2H, ArCH₂O), 7.43-7.10 (m, 10H, Ar), 7.91 (m, 1H,
NH), 8.24 (d, 1H, NH).
- 30 25 4c. A solution of the compound formed in Example 4b (0.023 g,
0.049 mmol) in ethanol (5 mL) is treated with 10% Pd/C (0.010
g) and pyridine (2 drops) under hydrogen atmosphere. After
32 hours, the reaction mixture is filtered to remove catalyst
and the filtrate evaporated to a yellow oil and placed under
high vacuum to give a gum. Trituration with diethylether
produces an off-white solid, which is collected by filtration
and dried under a nitrogen flow to give the final compound.
- 35 25 1H NMR (MeOH-d4) δ 1.91-1.35 (m, 6H, CCH₂CH₂CH₂C), 2.30-2.10
(m, 4H, CH₂CHCO and CH₂COOH), 2.62 (m, 1H, CH₂CHCO), 2.70 (s,

3H, NCH₃), 3.15 (m) and 2.95 (m), (4H), 4.52 (t, 1H, NCHCO), 7.36-7.15 (m, 5H, Ar).

EXAMPLE 5

5

N-[*(2R*)-2-[2'-(Hydroxymino)-2'-(oxo)ethyl]-6-(propylamino)-6-(oxo)hexanoyl-L-phenylalanine N-methylamide

10 5a. Synthesis of N-[*(2R*)-2-(tert-Butoxycarbonylmethyl)-5-(carboxy)pentanoyl-L-phenylalanine N-methylamide

Pyridinium dichromate (0.658 g, 1.7 mmol) is added to a solution of the compound formed in Example 3a (0.203 g, 0.5 mmol) in DMF (2 mL) under a nitrogen atmosphere. The resulting mixture is stirred at room temperature for 16 hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The combined ethyl acetate layers are washed with water and brine. The ethyl acetate is separated, dried (Na₂SO₄), and evaporated. The gummy crude product (0.18 g) without any further purification is used in the next step.

25 ¹H NMR (CDCl₃) δ 1.10 - 1.80 (m, 13H, CCH₂CH₂C, t-butyl H), 2.20 - 2.80 (m, 8H), 3.00 - 3.20 (m, 2H), 4.68 (q, 1H, NCH), 6.50 (s, 1H), 7.00 - 7.60 (m, 5H, ArH).

30 5b. Synthesis of N-[*(2R*)-2-(tert-Butoxycarbonylmethyl)-6-(propylamino)-6-(oxo)hexanoyl-L-phenylalanine N-methylamide

A solution of the acid of example 5a (0.18 g, 0.43 mmol) and n-propylamine (0.1 g, 1.7 mmol) in dry DMF (5 mL) under nitrogen is cooled to -5°C and treated dropwise with diethylcyanophosphonate (0.07 g, 0.43 mmol) followed by triethylamine (0.86 g, 0.85 mmol). The reaction mixture is stirred at 0°C for 1 hour, then slowly allowed to come to room temperature during 1 hour. The reaction mixture is stirred at room temperature for 3 hours, then diluted with

water and extracted with ethyl acetate and ether solvents. The combined organic layers are sequentially washed with 5% citric acid, saturated NaHCO₃, water, and brine. The organic layer is separated, dried (Na₂SO₄), and evaporated. The residue is triturated with diethyl ether to produce a white solid. The solid is collected by filtration and air dried to give 0.065 g. The overall yield for two steps is 28.3%.

10 ¹H NMR (CDCl₃) δ 0.91 (t, 2H, CH₂CH₃), 1.30 - 1.80 (m, 15H, CCH₂CH₂C, CH₂CH₃, t-butyl H), 2.13 (t, 2H, CH₂CON), 2.25 - 2.60 (m, 3H, CH₂COO and CHCO), 2.71 (d, 3H, NCH₃), 3.05 - 3.30 (m, 4H, NHCH₂Ar and CH₂Ar), 4.62 (q, 1H, NCH), 5.98 (br signal, 1H, NH), 6.38 (br signal, 1H, NH), 6.70 (br signal, 1H, NH), 7.10 - 7.40 (m, 5H, ArH).

15

5c. Synthesis of N-[*(2R*)-2-(Carboxymethyl)-6-(propylamino)-6-(oxo)hexanoyl-L-phenylalanine N-methylamide

A solution of the compound formed in example 5b (0.06 g, 0.13 mmol) in trifluoroacetic acid (3.5 mL), and water (1.5 mL) is stirred at room temperature for 4 hours. The solvents are removed on a rotary evaporator. The residue is treated with acetonitrile and evaporated (three times) in order to azeotrope water. The white solid obtained is placed on a high vacuum pump for 1 hour. The product is triturated with diethyl ether. The product is collected by filtration and air dried to give 0.045 g (85.4% yield) of a white solid.

30 ¹H NMR (MeOH-d₄) δ 0.70 (t, 2H, CH₂CH₃), 1.10 - 1.5 (m, 6H, CH₂CH₃ and CCH₂CH₂C), 1.91 (t, 2H, CH₂CON), 2.05 - 2.60 (m, 6H, CH₂COO, CHCO and NCH₃), 2.70 - 3.00 (m, 4H, NHCH₂ and CH₂Ar), 4.30 (q, 1H, NCH), 6.90 - 7.30 (m, 5H, ArH), 7.60 (m, 1H), 8.00 (d, 1H).

Mass (FAB): 406 (MH⁺)

5d. Under a nitrogen atmosphere, the carboxylic acid compound formed in example 5c (0.04 g, 0.1 mmol) in dry THF (10 mL) is cooled to -15°C (solubility of the acid seems to be low in THF, at low temperature some acid precepitated out) and
5 treated with N-methylmorpholine (0.02 g, 0.2 mmol). After five minutes, isobutylchloroformate, (0.027 g, 0.2 mmol) is added dropwise and the reaction mixture is stirred for 35 minutes. O-(trimethylsilyl)hydroxylamine (0.126 g, 1.2 mmol) is added dropwise. The reaction mixture is stirred at -15°C
10 for 1 hour, followed by 1 hour at 0°C, then 1.5 hours at room temperature. The reaction mixture is filtered and the precipitate washed several times with dichloromethane. The residue is once again taken into dichloromethane and stirred for 2 hours. The white solid is collected by filtration and
15 dried in vacuuo to give the final product.

¹H NMR (MeOH-d₄) δ 0.70 (t, 3H, CH₂CH₃), 1.10 - 1.50 (m, 6H, CH₂CH₃ and CCH₂CH₂C), 1.80 - 2.10 (m, 4H, CH₂COO and CH₂CON), 2.30 - 2.60 (m, 4H, CHCO, NCH₃), 2.65- 3.05 (m, 4H, NHCH₂ and CH₂Ar), 4.30 (d, 1H, NCH), 6.90 - 7.30 (m, 5H, ArH).
20 Mass (FAB): 421 (MH⁺)

EXAMPLE 6

25 N-[2R]-2-[2'-(Hydroxyamino)-2'(oxo)ethyl]-6-
(hydroxy)heptanoyl-L-phenylalanine N-methylamide

6a. Synthesis of (4S)-4-Benzyl-3-[2'R)-2'-(tert-butoxy-
carbonylmethyl)-6'-(hydroxy)hexanoyl-2-oxazolidone.
30 The compound of example 1e [1.5g, 3 mmol] is dissolved in absolute ethanol and enough EtOAc to get the material into solution. 1g of 20% Palladium Hydroxide on carbon (Pd(OH)₂/C) and 0.28 mL [30 mmol] of 1,4-cyclohexadiene are added, and the reaction is warmed slowly to 65°C while stirring under a N₂ atmosphere. A vigorous frothing occurs
35 shortly after (H₂ generation). The reaction is stirred for

12 hrs. The reaction is cooled and filtered through Celite, and the Celite is washed with EtOAc. The solvent is evaporated, and the residue solidified. The solid is recrystallized from Et₂O/hexane, which affords 1.04 g of a white fluffy solid product (85% yield).

5 ¹H-NMR (CDCl₃): δ 1.4-1.8 (s and m, 16H, t-butyl, -OH, and -(CH₂)₃), 2.54 (dd, 1H, -COCH₂CHCO), 2.84 (overlapping dd, 2H, one -COCH₂CHCO and one -CHCH₂Ph), 3.4 (dd, 1H, -CHCH₂Ph), 3.68 (t, 2H, -CH₂OH), 4.22 (m, 3H, oxazol. ring -CH₂ and -CH₂CHCO), 4.72 (m, 1H, oxazol. ring -CH), 7.35 (m, 5H, Ar).

10 6b. Synthesis of (4S)-4-Benzyl-3-[(2'R)-2'-(tert-butoxy-carbonylmethyl)-5'-(formyl)pentanoyl]-2-oxazolidone

15 Oxalyl chloride [0.231 mL, 2.7 mmol] is dissolved in 10 mL anhyd. CH₂Cl₂ and cooled to -78°C under a N₂ atmosphere. 0.192 mL [2.7 mmol] of anhydrous dimethyl sulfoxide (DMSO) in 5 mL CH₂Cl₂ is added dropwise via syringe; this is accompanied by the evolution of CO₂ and CO bubbles. The reaction is stirred at -78°C for 30 min. 1.0 g [2.46 mmol] of the compound of example 6a in 10 mL of CH₂Cl₂ is then added dropwise via syringe, which causes the reaction to become cloudy white. Stirring is continued for 1 hr. at -78°C, then 1.58 mL [11 mmol] of triethylamine (Et₃N) in 10 mL of CH₂Cl₂ is added dropwise via syringe and the reaction warmed to room temperature. During this time, the reaction becomes increasingly clearer. The reaction is partitioned between H₂O and CH₂Cl₂ and the organic layer washed with 5% NaHCO₃, 5% citric acid, H₂O, and brine, then dried over Na₂SO₄. The solvent is removed and the residue is flash chromatographed to give 0.81 g of a gummy solid (81%).

20 ¹H-NMR (CDCl₃): δ 1.4-1.8 (s and m, 13H, t-butyl and -(CH₂)₂), 2.54 (overlapping t and dd, 3H, -CH₂CHO and one -COCH₂CHCO), 2.8 (overlapping dd, 2H, one -COCH₂CHCO and one -CHCH₂Ph), 3.36 (dd, 1H, one -CHCH₂Ph), 4.2 (m, 3H, oxazol.

ring -CH₂ and -CH₂CHCO), 4.7 (m, 1H, oxazol. ring -CH), 7.3 (m, 5H, Ar), 9.78 (s, 1H, CHO).

6c. Synthesis of (4S)-4-Benzyl-3-[(2'R)-2'-(tert-butoxy-

5 carbonylmethyl)-(6'RS)-6'-(hydroxy)heptanoyl]-2-
oxazolidone The compound of example 6b [1.33 g, 33 mmol] is dissolved in dry/distilled THF and cooled to -15°C under a N₂ atmosphere. A solution of 3M solution of methyl magnesium bromide in ether [1.1 mL, 33 mmol] is added dropwise with stirring. Stirring is continued for 1 hr. at -15°C, then the reaction is warmed to room temperature and quenched with a aqueous NH₄Cl solution. The THF is evaporated and the reaction is extracted with EtOAc. The combined EtOAc layers are then washed with 5% NaHCO₃, 5% citric acid, and brine, 10 and then dried over Na₂SO₄. Flash chromatography is used to 15 isolate 250 mg of the desired secondary alcohol (18% yield).

1H- NMR (CDCl₃): δ 1.23 (d, 3H, CHCH₃), 1.4-1.8 (s and m, 16H, t-butyl, -OH, and -(CH₂)₃), 2.55 (dd, 1H, one -COCH₂CHCO), 2.82 (overlapping dd, 2H, one -COCH₂CHCO and one -CHCH₂Ph), 20 3.39 (dd, 1H, one -CHCH₂Ph), 3.84 (m, 1H, CHOH, 4.22 (m, 3H, oxazol. ring -CH₂ and -CH₂CHCO), 4.72 (m, 1H, oxazol. ring -CH), 7.3-7.45 (m, 5H, Ar). No peak doubling due to the presence of diasteromers was observed.

25 6d. Synthesis of (2R)-2-(tert-Butoxycarbonyl)methyl-(6RS)-

6-(hydroxy)heptanoic acid The compound of example 6c [0.25g, 0.6 mmol] is dissolved in 2.5 mL of a 4:1 THF/H₂O solution and cooled to ~2°C, but no lower, under a N₂ atmosphere. Dropwise and with stirring, 30% aqueous H₂O₂, 0.265 mL [0.09 g, 2.6 mmol] is added. After stirring 5 minutes, a solution of LiOH•H₂O [0.042 g, 1.0 mmol] in 1 mL H₂O is added slowly. During these additions, the temperature of the reaction is maintained below 3-4° C. The temperature 30 of the reaction is slowly allowed to come to room temperature 35

(30 min), and stirred for 1 hr. The reaction is cooled and quenched slowly with Na₂SO₃ [0.126 g, 1.0 mmol] in 2.5 mL H₂O. The THF is evaporated (keeping the temperature low so as not to racemize stereo centers) and the basic, aqueous mixture remaining is extracted with methylene chloride to remove free benzyl oxazolidinone which can be recrystallized and recycled for further use. The basic layer is then cooled and acidified with the slow addition of concentrated HCl (pH 1). The cloudy mixture is then extracted with EtOAc. The EtOAc extracts are dried over Na₂SO₄ and evaporated to give 0.15 g of pure acid (96% yield).

¹H-NMR (CDCl₃): δ 1.25-1.85 (m, 16H, OH, CCH₂CH₂CH₂C, t-butyl H), 2.25-2.68 (two dd, s, COCH₂), 2.73-2.85 (m, 1H, CHCOO), 3.70-3.90 (m, 1H, CHOH).

6e. Synthesis of N-[*(2R)-2-(tert-Butoxycarbonylmethyl)-(6RS)-6-hydroxy-heptanoyl]-L-phenylalanine N-methyl-amide* A solution of the compound of example 6d [0.10 g, 0.384 mmol] and L-phenylalanine N-methylamide TFA salt (0.136 g, 0.768 mmol) in dry dimethylformamide (2 mL) under nitrogen is cooled to -6°C and treated dropwise with diethylcyanophosphonate [0.062 g, 0.384 mmol] followed by triethylamine [0.116 g, 1.15 mmol]. The reaction mixture is stirred at 0°C for 1hr, allowed to warm to room temperature over 1 hr, then stirred for two additional hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The combined ethyl acetate layers are sequentially washed with 5% citric acid, saturated sodium bicarbonate, water, and brine. The ethyl acetate is separated, dried (Na₂SO₄), and evaporated. The residue is purified by silica gel column chromatography using 10% methanol in ethyl acetate as the eluent. The appropriate fraction yields 0.15 g (93% yield) of product.

5 ¹H- NMR (CDCl₃): δ 1.14 (d, 3H, -CHCH₃), 1.14-1.7 (m and s, 15H, t-butyl and -(CH₂)₃), 2.27-2.6 (m, 3H, -COCH₂CHCO, -COCH₂CHCO), 2.68 (d, 3H, NCH₃), 3.07 (d, 2H, -CHCH₂Ph), 3.82 (m, 1H, CHOH), 4.68 (q, 1H, NHCHCO), 6.32 (d, 1H, -NHCH₃), 6.63 (d, 1H, -NHCH), 7.24 (m, 5H, Ar). Peak doubling due to diastereomers was observed for -CHCH₃ and -NHCH₃ peaks.

10 6f. Synthesis of N-[*(2R*)-2-(Carboxymethyl)-(*6RS*)-6-(hydroxy)heptanoyl-L-phenylalanine N-methylamide The compound of example 6e [0.13 g, 0.39 mmol] is dissolved in 7 mL of trifluoroacetic acid (TFA) and 3 mL H₂O and stirred at room temperature until the t-butyl ester is consumed (followed by TLC). The TFA/H₂O is then evaporated and the residue triturated in Et₂O until a white solid is formed. 15 The solid is filtered, washed with fresh Et₂O, and dried in vacuo. 0.05 g of the acid as a white powder is obtained (44% yield).

20 ¹H- NMR (CD₃OD): δ 1.1 (d, 3H, -CHCH₃), 1.15-1.6 (m, 6H, -(CH₂)₃), 2.25 (2 dd, 2H, -CH₂COOH), 2.63 (overlapping m and s, 4H, -COCH₂CHCO and -NCH₃), 2.9 and 3.17 (2 dd, 2H, -CH₂Ph), 3.61 (m, 1H, CHOH), 4.49 (q, 1H, NHCHCO), 7.3 (m, 5H, Ar).

25 6g. The compound of example 6f [0.025 g, 0.07 mmol] is dissolved in 5 mL dry/distilled THF and cooled to -15°C under a N₂ atmosphere. N-methyl morpholine [8.6 μL, 0.077 mmol] is added via syringe with stirring, followed by 10 μL [0.077 mmol] of isobutylchloroformate. The solution becomes slightly cloudy. The reaction is stirred for 30 min. at -15°C, then 17 μL [0.14 mmol] of O-trimethylsilyl hydroxyl amine is added. After stirring for 1.5 hrs. the reaction is poured onto 5 mL of 5% NaHCO₃ then extracted with EtOAc. The organic layer is separated and washed with 5% citric acid, H₂O, and brine,

then dried over Na₂SO₄. The solvent is evaporated to give 0.01 g of hydroxamate (37% yield).

5 ¹H- NMR (CD₃OD): δ 1.1 (d, 3H, -CHCH₃), 1.15-1.6 (m, 6H, -(CH₂)₃), 2.15 (2 dd, 2H, -CH₂COOH), 2.63 (overlapping m and s, 4H, -COCH₂CHCO and NCH₃), 2.9 and 3.17 (2 dd, 2H, -CH₂Ph), 3.61 (m, 1H, CHOH), 4.49 (q, 1H, NHCHCO), 7.3 (m, 5H, Ar).

EXAMPLE 7

10 Alternative route to

N-[*(2R*)-2-(tert-Butoxycarbonylmethyl)-(6RS)-6-hydroxyheptanoyl-L-phenylalanine N-methylamide

15 7a. Synthesis of N-[*(2R*)-2-(tert-Butoxycarbonylmethyl)-6-(hydroxy)hexanoyl-L-phenylalanine N-methylamide The compound obtained in example 1g [2.0 g, 4 mmol] in 20 mL absolute EtOH is treated with 0.75 g 20% Pd(OH)₂/C and 3.8 mL [40 mmol] of 1,4-cyclohexadiene. The reaction is heated slowly to 65°C and stirred as such for ~20 hrs. The reaction is cooled and filtered through Celite. The Celite is washed with EtOAc, and the combined filtrates evaporated. The residue is flash chromatographed, resulting in a white solid [1.14 g, 70% yield].

25 ¹H- NMR (CDCl₃): δ 1.3-1.7 (m and s, 15H, t-butyl and -(CH₂)₃), 2.35-2.8 (m, 3H, -COCH₂CHCO and -COCH₂CHCO), 2.74 (d, 3H, NCH₃), 3.14 (2 d, 2H, -CHCH₂Ph), 3.64 (m, 2H, -CH₂OH), 4.62 (q, 1H, NHCHCO), 6.35 (d, 1H, -NHCH₃), 6.71 (d, 1H, -NHCH), 7.3 (m, 5H, Ar).

30 7b. Synthesis of N-[*(2R*)-2-(tert-Butoxycarbonylmethyl)-5-(formyl)pentanoyl-L-phenylalanine N-methylamide The compound of example 7a [0.05 g, 0.12 mmol] and 0.06 g, [0.24 mmol] of pyridinium chlorochromate (PCC) are dissolved in 10 mL of anhydrous CH₂Cl₂ under a N₂ atmosphere and stirred at

room temperature. The reaction is followed by TLC until the alcohol is consumed. EtOAc is then added to precipitate PCC salts, and the reaction is filtered through Celite several times. The solvent is evaporated and the residue flash chromatographed to afford 0.07 g (47%) of the aldehyde as a
5 gummy solid.

1H- NMR (CDCl₃): δ 1.4-1.75 (m and s, 13H, t-butyl and -CH₂CH₂), 2.4-2.75 (m, 5H, -COCH₂CHCO, -COCH₂CHCO, -CH₂CHO),
10 2.8 (d, 3H, NHCH₃), 3.2 (2 dd, 2H, -CH₂Ph), 4.66 (q, 1H, NHCHCO), 6.18 (d, 1H, -NHCH₃), 6.63 (d, 1H, -NHCH), 7.3 (m, 5H, Ar), 9.8 (s, 1H, CHO).

15 7c. Synthesis of N-[(2R)-2-(tert-Butoxycarbonylmethyl)-
(6RS)-6-hydroxy-heptanoyl-L-phenylalanine N-methyl-
amide Titanium isopropoxide [0.211 g, 0.74 mmol] is dissolved in 5 mL dry/distilled THF and cooled to -10°C under a N₂ atmosphere. A solution of 1.0M titanium (IV) chloride in CH₂Cl₂ [0.25 mL, 0.25 mmol] is then added dropwise via syringe. The reaction is then warmed to room temperature and stirred 1.5 hours. The reaction is cooled to -78°C and 0.71 mL [0.98 mmol] of 1.4M methyl lithium in Et₂O is added via syringe. The reaction becomes red in color, and upon warming slowly to room temperature, lithium chloride (LiCl) precipitates from the reaction, causing it to also be cloudy.
20 After 1 hour, stirring is stopped and the LiCl is allowed to settle. The solution of triispropoxymethyl titanium is again cooled to -78°C then transferred slowly via syringe to a dry/distilled THF solution (7 mL) of 0.1 g [0.25 mmol] of the compound formed in example 7b cooled to -78°C under a N₂ atmosphere. The reaction is warmed slowly to 0°C, stirred
25 for 1 hour, then quenched with dilute aqueous HCl. The THF is evaporated and the aqueous layer extracted with EtOAc.
30

The organic layer is washed with H₂O and brine, and then dried over Na₂SO₄. Flash chromatography is used to isolate 0.01 g of the desired secondary alcohol (10% yield).

5 ¹H-NMR (CDCl₃): δ 1.14 (d, 3H, -CHCH₃), 1.14-1.7 (m and s, 15H, t-butyl and -(CH₂)₃), 2.27-2.6 (m, 3H, -COCH₂CHCO, -COCH₂CHCO), 2.68 (d, 3H, NCH₃), 3.07 (d, 2H, -CHCH₂Ph), 3.82 (m, 1H, CHOH), 4.68 (q, 1H, NHCHCO), 6.32 (d, 1H, -NHCH₃), 6.63 (d, 1H, -NHCH), 7.24 (m, 5H, Ar). Peak doubling due to
10 diastereomers was observed for -CHCH₃ and -NHCH peaks.

EXAMPLE 8

15 (2S)-N-2-[2'R)-2'-(2''-(Hydroxymino)-2'''-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyllamino-3,3-dimethylbutanoic acid N-methylamide

8a. Synthesis of (2S)-N-2-[2'R)-2'-(tert-Butoxycarbonyl-methyl)-6'-(phenylmethoxy)hexanoyllamino-3,3-dimethylbutanoic acid N-methylamide A stirred solution of the compound of example 1f (0.3 g, 0.9 mmol) and (2S)-2-Amino-3,3-dimethylbutanoic acid N-methyl amide hydrochloride (0.187 g, 1 mmol) in 3 mL DMF under nitrogen is cooled to -5°C, and is treated with diethylcyanophosphonate (0.19 mL, 1.2 mmol), followed by dropwise addition of triethylamine (0.4 mL, 2.8 mmol). The reaction mixture is stirred cold for 2.5 hours, then at ambient temperature for 2.5 hours longer. The reaction mixture is then diluted with 30 mL of ethyl acetate, and washed sequentially with 5% citric acid solution, 5% sodium bicarbonate solution, and brine. The ethyl acetate is separated, dried over anhydrous sodium sulfate, filtered, and evaporated to 424 mg (91%) of a colorless oil, which can be used in the following step without further purification.

¹H NMR (CDCl₃): δ 1.00 (s, 9H, (CH₃)₃), 1.2-1.75 (m, 15H), 2.30 - 2.70 (m, 3H, COCH₂CHCO), 2.80 (d, 2H, NHCH₃), 3.45 (t, 2H, CH₂O), 4.25 (d, 1H, NCHCO), 4.50 (s, 2H, PhCH₂O), 6.15 (bs, 1H, NH), 6.55 (d, 1H, NH), 7.2 - 7.5 (m, 5H, Ar).

5

- 8b. Synthesis of (2S)-N-2-[2'R)-2'-(carboxymethyl)-6'-(phenylmethoxy)hexanoyllamino-3,3-dimethylbutanoic acid N-methylamide The compound of example 8a (424 mg, 0.9 mmol) is dissolved in a mixture of trifluoroacetic acid (3 mL) and water (1 mL), and stirred at ambient temperature for 3 hours. The solvents are evaporated, and the residue placed under high vacuum for 2 hours. The oily residue is purified by flash silica gel chromatography (2% methanol in CH₂Cl₂). Product containing fractions is evaporated to yield 295 mg (81%) of a white foam.

10

15

¹H NMR (CDCl₃): δ 0.95 (s, 9H, (CH₃)₃), 1.20 - 1.70 (m, 6H), 2.40 - 2.75 (m, 3H, COCH₂CHCO), 2.80 (d, 2H, NHCH₃), 3.40 (t, 2H, CH₂), 4.40 (d, 1H, NCHCO), 4.50 (s, 2H ArCH₂O), 6.70 (bs, 1H, NH), 7.23 - 7.6 (m, 6H, Ar & NH).

20

25

30

35

- 8c. To a -10°C stirred solution of the compound of example 8b (295 mg, 0.73 mmol) in 3 mL of dry distilled THF under nitrogen is added in one portion N-methylmorpholine (0.09 mL, 0.8 mmol). After stirring 5 minutes, the reaction mixture is treated dropwise with isobutylchloroformate (0.1 mL, 0.8 mmol), and the resultant suspension is stirred for 15 to 20 minutes. The reaction mixture is then treated with O-(trimethylsilyl)hydroxylamine (84 mg, 0.8 mmol), and the stirring continued for 2 hours at ice bath temperature, followed by 2 hours at ambient temperature. The reaction mixture is filtered, and the filtrate evaporated to a white foam. The foam is stirred overnight in 10 mL of diethyl ether, which produces the desired hydroxamate as a white solid (220 mg, 71%).

5 ¹H NMR (DMSO d₆): δ 0.90 (s, 9H, (CH₃)₃), 1.10 - 1.60 (m, 6H),
1.95 - 2.20 (m, 2H), 2.50 (d, 3H, NCH₃), 2.79 (m, 1H),
4.15 (d, 1H, COCHN), 4.40 (s, 2H, ArCH₂O), 7.20 - 7.40 (m,
5H, Ar), 7.67 (d, 1H, NH), 7.85 (bs, 1H, NH), 8.65 (s,
1H, OH).

EXAMPLE 9

10 (2S)-N-2-[(2'R)-2'-(2"--(Hydroxvamino)-2"--(oxo)ethyl]-
6'-(hydroxy)hexanoyllamino-3,3-dimethylbutanoic acid
N-methylamide

15 9a. Synthesis of (2S)-N-2-[(2'R)-2'-(tert-Butoxycarbonyl-
20 methyl)-6'-(hydroxy)hexanoyll-amino-3,3-dimethylbu-
25 tanoic acid N-methylamide Under a nitrogen atmosphere, a
solution of the compound formed in example 8a (1.5 g, 3.2
mmol) in ethanol (25 mL) is treated with 20% Pd(OH)₂ on C
(0.6 g) and 1,4-cyclohexadiene (10 mL). The mixture is heated
at 65° C for 16 hours at which point 0.5 g of 20% Pd(OH)₂ on
C and 1,4-cyclohexadiene (4 mL) is added and heating is
continued for another 5 hours. The reaction mixture is
cooled and the catalyst is collected via filtration. The
filtrate is evaporated to dryness and the residue is purified
by silica gel column chromatography using 5% methanol in
ethyl acetate as the eluent to give the desired product (0.85
g, 71% yield).

30 ¹H NMR(CDCI₃) δ 0.95 (s, 9H, t-butyl H), 1.15-1.80 (m, 15H,
CCH₂CH₂CH₂C and t-butyl H), 2.40 (dd, 1H, COCH₂CHCO), 2.50-
2.90 (m, 5H, NCH₃, COCH₂CHCO), 3.45-3.75 (m, 2H, CH₂O), 4.40
(d, 1H, NCH), 6.70 (m, 1H, NH), 7.26 (m, 1H, NH).

35 9b. Synthesis of (2S)-N-2-[(2'R)-2'-(Carbonylmethyl)-6'-
(hydroxy)hexanoyllamino-3,3-dimethylbutanoic acid N-
methylamide The compound of example 9a (0.6 g, 1.6 mmol)

is dissolved in 10 mL of a 7:3 trifluoroacetic acid-water mixture and stirred at room temperature for 4.0 hours. The solvents are removed on a rotary evaporator and the residue is treated with acetonitrile and evaporated (three times) in order to azeotrope water. The colorless gummy product (0.635 g) is dried on a high vacuum pump. The product does not solidify, perhaps due to remaining impurities and trifluoroacetic acid. The compound without any further purification is used in next reaction.

¹⁰ ^1H NMR (MeOH-d₄) δ 0.95 (s, 9H, t-butyl H), 1.20-1.85 (m, 6H, CCH₂CH₂CH₂C), 2.35 -3.00 (m, 6H, NCH₃, COCH₂CHCO), 3.64 (m, 2H, CH₂O), 4.45 (d, 1H, NCH).

¹⁵ 9c. Under a nitrogen atmosphere, the compound of example 9b (0.143 g, 0.4 mmol), dissolved in dry tetrahydrofuran (10 mL), is cooled to -15°C and treated with N-methylmorpholine (0.081 g, 0.8 mmol). After 5 min, isobutylchloroformate (0.109 g, 0.8 mmol) is added dropwise and the reaction mixture is stirred for 15 min. O-(trimethylsilyl)hydroxyl-²⁰ amine (0.25 g, 2.4 mmol) is added dropwise. The reaction mixture is stirred at -15°C for 1 hour, followed by 1 hour at 0°C, then 30 minutes at room temperature. The reaction mixture is filtered and the filtrate is evaporated to dryness. The crude product is purified by preparative thin layer chromatography using 25% methanol in ethyl acetate as eluent, giving a colorless solid product (0.068 g, 45%²⁵ yield).

³⁰ ^1H NMR (MeOH-d₄) δ 0.77 (s, 9H, t-butyl H), 0.90-1.50 (m, 6H, CCH₂CH₂CH₂C), 1.90-2.25 (two dd's, 2H, CH₂CO), 2.50 (s, 3H, NCH₃), 2.56-2.78 (m, 1H, CHCO), 3.30 (t, 2H, CH₂O), 3.98 (s, 1H, NCH).

EXAMPLE 10

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-5-(phenylmethoxy)pentanoyl-L-phenylalanine N-methylamide

5

Synthesis using a procedure analogous to that of Example 2 results in a compound having the following analysis:

¹H-NMR (CD₃OD): δ 1.24-1.36 (m, 4H, -(CH₂)₂), 1.95 (2 dd, 2H, -CH₂CONHOH), 2.5 (overlapping s and m, 4H, -NCH₃ and -CHCH₂CONHOH), 2.75 and 2.98 (2 dd, 2H, -CCH₂Ph), 3.27 (t, 2H, -CH₂OCH₂Ph), 4.33 (overlapping s and q, 3H, -OCH₂Ph and -NCHCO), 7.06-7.33 (m, 10H, Ar).

15

EXAMPLE 11

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-7-(phenylmethoxy)heptanoyl-L-phenylalanine N-methylamide)

20 Synthesis using a procedure analogous to Example 2 results in a compound which produces the following analysis:

¹H-NMR (CD₃OD): δ 1.01-1.5 (m, 8H, -(CH₂)₄), 1.98-2.21 (2 dd, 2H, -CH₂CONHOH), 2.52 (m, 1H, -CHCH₂CONHOH), 2.59 (s, 3H, -NCH₃), 2.86 and 3.09 (2 dd, 2H, -CCH₂Ph), 3.38 (t, 2H, -CH₂OCH₂Ph), 4.41 (overlapping s and q, 3H, -OCH₂Ph and -NCHCO), 7.05-7.28 (m, 10H, Ar).

30

EXAMPLE 12

N-[(2'R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(4'-oxobutylamino)hexanoyl-L-phenylalanine N-methylamide

12a. Synthesis of (4S)-4-Benzyl-3-[(2'R)-2'-(tert-butoxy-carbonylmethyl)-6'-(methanesulfonyloxy)hexanoyl-2-oxazolidone 0.5 g [1.23 mmol] of the product formed in example 6a, 0.24 mL [1.72 mmol] of Et₃N, and 0.03 g of 4-

dimethylamino pyridine [0.246 mmol] are dissolved in 10 mL dry CH_2Cl_2 and cooled to 0°C under N_2 . Methanesulfonyl chloride [0.105 mL, 1.35 mmol] is then added dropwise via syringe with stirring. The reaction is stirred at 0°C for 2 hrs. then warmed to room temperature and quenched with H_2O .
5 The layers were separated and the organic layer was washed with 5% NaHCO_3 , 5% citric acid, H_2O , and brine, then dried over Na_2SO_4 . Evaporation of the solvent affords 0.57 g of the desired product (96%) as a colorless oil. No further
10 purification is done.

$^1\text{H-NMR}$ (CDCl_3): δ 1.41-1.84 (m and s, 15H, -t-Bu and $-(\text{CH}_2)_3$),
2.48 (dd, 1H, $-\text{CH}_2\text{COOtBu}$), 2.84 (2 overlapping dd, 2H, one
15 $-\text{CH}_2\text{COOtBu}$ and one $-\text{CHCH}_2\text{Ph}$), 3.02 (s, 3H, $-\text{SO}_2\text{CH}_3$), 3.34 (dd, 1H, $-\text{CHCH}_2\text{Ph}$), 4.13-4.28 (m, 5H, $-\text{CH}_2\text{OSO}_2$, oxazol. ring
 $-\text{CH}_2$, and $-\text{CHCH}_2\text{COOtBu}$), 4.69 (m, 1H, oxazol. ring -CH),
7.23-7.39 (m, 5H, Ar).

12b. Synthesis of (4S)-4-Benzyl-3-[(2'R)-2'-(tert-butoxy-
20 carbonylmethyl)-6'-(azido)-hexanoyl]-2-oxazolidone

The compound of example 12a [2.1 g, 4.34 mmol] and tetrabutylammonium iodide [1.6 g, 4.34 mmol] are dissolved in 20 mL toluene. A sodium azide solution [2.8 g, 43 mmol] in 20 mL H_2O is then added and the two-phase reaction stirred vigorously at 70°C for 17 hours under N_2 . The reaction is cooled, the layers separated, and the aqueous layer extracted with EtOAc. The EtOAc and toluene layers are combined and washed with 5% NaHCO_3 , 5% citric acid, H_2O , and brine, then dried over Na_2SO_4 . The solvent is evaporated, leaving an oil residue which solidifies. The solid is recrystallized from Et₂O/hexane which yields 1.5 g of the desired azide (80%) as white crystals.
25
30

$^1\text{H-NMR}$ (CDCl_3): δ 1.45-1.75 (m and s, 15H, -t-Bu and $-(\text{CH}_2)_3$),
2.47 (dd, 1H, $-\text{CH}_2\text{COOtBu}$), 2.78 (2 overlapping dd, 2H, one
35

-CH₂COOtBu and one -CHCH₂Ph), 3.28 (t, 2H, -CH₂N₃), 3.34 (dd, 1H, -CHCH₂Ph), 4.17 (m, 3H, oxazol. ring -CH₂, and -CHCH₂COOtBu), 4.67 (m, 1H, oxazol. ring -CH), 7.23-7.37 (m, 5H, Ar).

5

12c. Synthesis of (2R)-2-(tert-Butoxycarbonylmethyl)-6-(azido)hexanoic acid The compound of example 12c [0.3 g, 0.7 mmol] is dissolved in 15 mL of a 4:1 THF/H₂O solution and cooled to ~2°C, but not below, under a N₂ atmosphere. A 10 solution of 30% aqueous H₂O₂ [0.285 mL, 2.8 mmol] is then added via syringe while maintaining the temperature below 5°C. After stirring 5 minutes, a solution of LiOH·H₂O [0.046 g, 1.12 mmol] in 2 mL H₂O is added slowly via syringe. Some 15 gas evolution is observed. The reaction is stirred for 10 minutes, then warmed to room temperature and stirred 1 hour. A solution of Na₂SO₃ [0.35 g, 2.8 mmol] in 2 mL H₂O is then 20 added dropwise; some heat is evolved during this process, so the reaction is cooled. After stirring ~20 minutes, the THF is evaporated (below 30°C) and the remaining basic layer is extracted with EtOAc. These EtOAc extracts contain free (S)-(-)-4-benzyl-2-oxazolidone which is recrystallized and recycled for further use. The basic layer is cooled and acidified with the slow addition of concentrated aqueous HCl to a pH 2-3. The cloudy mixture is extracted with EtOAc, and 25 the EtOAc dried over Na₂SO₄ and evaporated to give 0.17 g of pure acid (90% yield).

30 ¹H-NMR (CDCl₃): δ 1.39-1.7 (m and s, 15H, -t-Bu and -(CH₂)₃), 2.4 (dd, 1H, -CH₂COOtBu), 2.65 (dd, 2H, -CH₂COOtBu), 2.82 (m, 1H, -CHCH₂COOtBu), 3.29 (t, 2H, -CH₂N₃).

35 12d. Synthesis of N-[(2R)-2-(tert-Butoxycarbonylmethyl)-6-(azido)hexanoyl]-L-phenylalanine N-methylamide The compound of example 12c [0.17 g, 0.64 mmol] and L-phenylalanine methyl amide TFA salt [0.182 g, 0.7 mmol] are

dissolved in 10 mL dry DMF and cooled to -10°C under a N₂ atmosphere. Diethylcyanophosphonate [0.101 mL, 0.67 mmol], followed by Et₃N [0.264 mL, 1.9 mmol], are added dropwise via syringe. The reaction is stirred for 1 hour at -10°C then at room temperature for 2 hours. The reaction is diluted with 30 mL H₂O and extracted with EtOAc. The combined EtOAc layers are then washed with 5% NaHCO₃, 5% citric acid, H₂O, and brine, then dried over Na₂SO₄. The solvent is evaporated, and the residue flash chromatographed, affording 1.05 g of the coupled product (74% yield).

¹H-NMR (CDCl₃): δ 1.4-1.68 (m and s, 15H, -t-Bu and -(CH₂)₃), 2.3-2.58 (m, 3H, -CHCH₂COOtBu), 2.7 (d, 3H, -NCH₃), 3.09 (2 dd, 2H, -CHCH₂Ph), 3.21 (t, 2H, -CH₂N₃) 4.51 (q, 1H, NCHCO), 5.81 (d, 1H, -NH), 6.35 (d, 1H, NH), 7.19-7.33 (m, 5H, Ar).

12e. Synthesis of N-[(2R)-2-(tert-Butoxycarbonylmethyl)-6-(aminohexanoyl)-L-phenylalanine N-methylamide. The compound of example 12d [0.083 g, 0.19 mmol] in 15 mL dry/distilled THF is hydrogenated (0.1 g 10% Pd/C, 30 psi, 25°C, 1.2 hours.) on a Parr shaker apparatus. After this time, the reaction is filtered through Celite and the Celite washed with EtOH. The combined filtrates are evaporated, leaving 0.084 g of a gummy solid. No further purification is done (>90% yield).

¹H-NMR (CD₃OD): δ 1.1-1.5 (m and s, 15H, -t-Bu and -(CH₂)₃), 2.15-2.41 (m, 3H, -CHCH₂COOtBu), 2.47-2.61 (overlapping s and t, 5H, -CH₂NH₂ and -NCH₃), 2.9 and 3.05 (2 dd, 2H, -CHCH₂Ph), 4.41 (t, 1H, -NCHCO), 7.07-7.26 (m, 5H, Ar).

12f. Synthesis of N-[(2R)-2-(tert-Butoxycarbonylmethyl)-6-(4'-oxobutylamino)-hexanoyl-L-phenylalanine N-me-

thylamide The compound of example 12e [0.394 g, 0.97 mmol] is dissolved in 15 mL dry DMF and cooled to -10°C under a N₂ atmosphere. Triethylamine [0.203 mL, 1.46 mmol], followed by butyroyl chloride [0.111 mL, 1.07 mmol] are added dropwise via syringe. The reaction becomes slightly cloudy white. The reaction is stirred 20 minutes at -10°C then warmed to room temperature and stirred 1.5 hours. The reaction mixture was treated with 40 mL H₂O and then extracted with EtOAc. The combined extracts were washed with 5% NaHCO₃, 5% citric acid, H₂O, and brine, then dried over Na₂SO₄. The solvent is evaporated, leaving a fluffy white solid which is recrystallized from CH₃CN/Et₂O and washed with cold Et₂O. This affords 0.29 g of the desired acyl amine (63% yield).

15 ¹H-NMR (CDCl₃): δ 0.95 (t, 3H, -CH₂CH₃), 1.2-1.71 (m and s, 17H, -t-Bu and -(CH₂)₄), 2.15 (t, 2H, -NCOCH₂), 2.27-2.59 (m, 3H, -CHCH₂COOtBu), 2.7 (d, 3H, -NCH₃), 3.09 (2 dd, 2H, -CHCH₂Ph), 3.21 (m, 2H, -CH₂NH), 4.51 (q, 1H, -NCHCO), 5.81 (broad s, 1H, -NH), 5.89 (broad s, 1H, -NH), 6.35 (d, 1H, -NH), 7.14-7.34 (m, 5H, Ar).

20 12g. **Synthesis of N-[2R]-2-(Carboxymethyl)-6-(4'-oxobutyl-amino)hexanoyl-L-phenylalanine N-methylamide** The compound of example 12f [0.15 g, 0.31 mmol] was dissolved in 10 mL of a 7:3 TFA/H₂O solution and stirred at room temperature until the t-butyl ester is consumed (followed by TLC). The TFA/H₂O is then evaporated, and the residue triturated in Et₂O, producing a white solid. The solid is filtered, washed with CH₃CN several times, and dried in vacuo. 0.125 g of the acid as a white powder are obtained (94% yield).

25 30 35 ¹H-NMR (CD₃OD): δ 0.87 (t, 3H, -CH₂CH₃), 1.02-1.63 (m, 8H, -(CH₂)₄), 2.08 (t, 2H, -NCOCH₂), 2.2-2.48 (2 dd, 2H, -CH₂COOH), 2.56 (overlapping s and m, 4H, -NCH₃ and

-CHCH₂COOH), 2.84-3.1 (overlapping t and 2 dd, 4H, -CH₂NH and -CHCH₂Ph), 4.41 (t, 1H, NCHCO), 7.02-7.27 (m, 5H, Ar).

12h. The compound of example 12g [0.08 g, 0.19 mmol] is dissolved
5 in ~5 mL dry DMF and cooled to -10°C under a N₂ atmosphere.
The reaction mixture is treated with N-methylmorpholine
[0.026 mL, 0.23 mmol], followed by isobutylchloroformate
[0.030 mL, 0.23 mmol] via syringe with stirring. The
solution becomes slightly cloudy. The reaction is stirred
10 for 30 min. at -10°C, then 0.058 mL [0.48 mmol] of O-
trimethylsilyl hydroxylamine is added via syringe and stirred
another 1.5 hours at -10°C. The reaction is warmed to room
temperature and the solvent evaporated. The gummy residue is
15 triturated in Et₂O, causing it to solidify. The solid is
triturated (CH₃CN) and recrystallized (MeOH/CH₃CN) several
times to give 0.065 g of hydroxamate as a white powder (78%
yield).

1H-NMR (CD₃OD): δ 0.85 (t, 2H, -CH₂CH₃), 0.99-1.61 (m, 8H,
20 -(CH₂)₄), 1.98-2.2 (overlapping t and 2 dd, 4H, -CH₂NHCOCH₂
and -CH₂CONHOH), 2.48-2.63 (overlapping s and m, 4H,
-CHCH₂CONHOH and -NCH₃), 2.81-3.11 (overlapping t and 2 dd,
4H, -CH₂NH and -CHCH₂Ph), 4.41 (q, 1H, NCHCO), 7.13-7.25 (m,
5H, Ar).

25

EXAMPLE 13

N-[^(2R)-(2-[2'-(Hydroxyamino)-2'(oxo)ethyl]-6-(phenoxy)-hexanoyl-L-phenylalanine N-methylamide

30

13a Synthesis of N-[^(2R)-(tert-butoxycarbonylmethyl)-6-(phenoxy)hexanoyl-L-phenylalanine N-methylamide
Diethyl azodicarboxylate [DEAD] (0.145 g, 0.837 mmol) is
added to a solution of triphenylphosphine (0.218 g, 0.837
mmol) in 20 mL of dry THF under a nitrogen atmosphere. The
35 mixture is stirred at room temperature for 15 minutes.

Phenol (0.078 g, 0.837 mmol), followed by the compound of example 3a (0.340 g, 0.837 mmol), is added and the resulting mixture stirred at room temperature for 18 hours. The solvent is evaporated to dryness and the residue is partitioned between water and methylene chloride. The methylene chloride layer is washed with water and brine, then purified by preparative thin-layer chromatography using 60% ethyl acetate in hexanes as eluent (0.255 g, 63.2% yield).

10 ^1H NMR (CDCl_3) δ 1.25-1.85 (m, 15H, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{C}$ and t-butyl H), 2.28-2.78 (m, 6H, NCH_3 , CH_2CO and CHCO), 3.00-3.20 (m, 2H, OCH_2Ph), 3.88 (t, 2H, OCH_2C), 4.54 (dd, 1H, NCH), 5.95 (m, 1H, NH), 6.45 (d, 1H, NH), 6.75-7.40 (m, 10H, ArH).

15 13b Synthesis of N-[*(2R*)-2-(carboxymethyl)-6-(phenoxy)hexanoyl-L-phenylalanine N-methylamide A solution of the compound of example 13a (0.213 g, 0.442 mmol) in trifluoroacetic acid (4 mL) and methylene chloride (6 mL) is stirred at room temperature for 5 hours. The solvents are removed on a rotary evaporator. The residue is placed on a high vacuum pump for 2 hours, then triturated with diethyl ether and hexanes to produce a colorless solid. The solid was collected by filtration and air dried (0.165 g, 87.7% yield).

25 ^1H NMR (CD_3OD) δ 1.00-1.60 (m, 6H, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{C}$), 2.05-2.60 (m, 6H, NCH_3 , CH_2CO and CHCO), 2.69-3.00 (two dd, 2H, CCH_2Ph), 3.66 (t, 2H, OCH_2C), 4.30 (dd, 1H, NCH), 6.60-7.20 (m, 10H, ArH).

30 13c Under a nitrogen atmosphere, the compound of example 13b (0.106 g, 0.25 mmol) is dissolved in dry THF (10 mL), and treated with N-methylmorpholine (0.076 g, 0.75 mmol) via syringe. The reaction mixture is cooled to -15° C and treated with isobutylchloroformate (0.051 mL, 0.37 mmol) via

syringe. After stirring the suspension for 15 minutes, O-(trimethylsilyl)hydroxylamine (0.105 mL, 1 mmol) is added and the reaction mixture is stirred at -15° C for 1 hour, followed by 1 hour at 0° C, then 30 minutes at room
5 temperature. The reaction mixture is filtered and the filtrate is evaporated to dryness. The crude product is purified by preparative thin-layer chromatography using 15% methanol in ethyl acetate as eluent (0.063 g, 57.4% yield).

10 ^1H NMR (CD_3OD) δ 0.90-1.60 (m, 6H, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{C}$), 1.80-2.14 (two dd, 2H, CH_2CO), 2.32-2.54 (m, 4H, NCH_3 , CHCO), 2.54 (dd) and 2.94 (dd) (2H CH_2Ph), 3.68 (t, 2H, OCH_2), 4.32 (dd, 1H, NCH), 6.6-7.7 (m, 10H, ArH).

15 EXAMPLE 14

N-[2R]-2-[2'-(Hydroxyamino)-2'(oxo)ethyl]-7-(phenoxy)-heptanoyl-L-phenylalanine N-methylamide

20 Synthesis using a procedure analogous to that of example 13 results in a compound having the following analysis.

25 ^1H NMR (CD_3OD) δ 0.8-1.60 (m, 8H, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}$), 1.84-2.10 (m, 2H, CH_2CO), 2.40-2.60 (m, 4H, NCH_3 , CHCO), 2.72 (dd) and 2.94 (dd) (2H, CH_2Ph), 3.72 (t, 2H, OCH_2), 4.30 (dd, 1H, CNH), 6.59-6.75 (m, 2H, ArH), 6.90-7.20 (m, 8H, ArH).

EXAMPLE 15

30 (2S)-N-2'-[(2'R)-2'-(2"--(Hydroxyamino)-2"--(oxo)ethyl)-6'-(2-phenethylamino)-6'(oxo)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide

35 Synthesis using a procedure analogous to that of example 5 results in a compound having the following analysis.

1H NMR (CD₃OD) δ 0.98 (s, 9H, t-butyl H), 1.30-1.7 (m, 6H), 2.10 (t, 2H, CH₂CO), 2.38 (dd, 1H), 2.50-2.65 (m, 2H), 2.76 (s, 3H, NCH₃), 2.80 (t, 2H, NHCH₂), 3.40 (t, 2H, CH₂Ph), 4.20 (d, 1H, NCH), 7.10-7.30 (m, 5H, ArH), 7.80 (d, 1H, NH).

5

EXAMPLE 16

(2S)-N-2'-(2'R)-2'-(2''-(Hydroxyamino)-2'''-(oxoethyl)-
6'-(4-methylphenoxy)hexanoyllamino-3,3-dimethylbutanoic
10 acid N-methylamide

Synthesis using a procedure analogous to that of example 13 results in a compound having the following analysis.

15 1H NMR (CD₃OD) δ 0.91 (s, 9H, t-butyl), 1.28-1.7 (m, 6H, (CH₂)₃), 2.1-2.32 (overlapping s and dd, 5H, PhCH₃ and CH₂CONHOH), 2.61 (s, 3H, NCH₃), 2.8 (m, 1H, CHCH₂CONHOH), 3.81 (t, 2H, CH₂OPh), 4.12 (d, 1H, NCH), 6.69 (d, 2H, ArH), 6.97 (d, 2H, ArH).

20

EXAMPLE 17

(2S)-N-2'-(2'R)-2'-(2''-(Hydroxyamino)-2'''-(oxoethyl)-
6'-(4-chlorophenoxy)hexanoyllamino-3,3-dimethylbutanoic
25 acid N-methylamide

Synthesis using a procedure analogous to that of example 13 results in a compound having the following analysis.

30 1H NMR (CD₃OD) δ 0.91 (s, 9H, t-butyl), 1.25-1.74 (m, 6H, (CH₂)₃), 2.1-2.32 (dd, 2H, CH₂CONHOH), 2.59 (s, 3H, NCH₃), 2.8 (m, 1H, CHCH₂CONHOH), 3.83 (t, 2H, CH₂OPh), 4.12 (d, 1H, NCH), 6.78 (d, 2H, ArH), 7.13 (d, 2H, ArH)

EXAMPLE 18

(2S)-N-2'-[(2'R)-2'-(2'-(Hydroxyamino)-2'-(oxo)ethyl-
6'-(3-methylphenoxy)hexanoyllamino-3,3-dimethylbutanoic
5 acid N-methylamide

Synthesis using a procedure analogous to that of example 13 results in a compound having the following analysis.

10 ^1H NMR (CD₃OD) δ 0.98 (s, 9H, t-butyl), 1.32-1.77 (m, 6H, (CH₂)₃), 2.16-2.4 (overlapping s and dd, 5H, PhCH₃ and CH₂CONHOH), 2.65 (s, 3H, NCH₃), 2.85 (m, 1H, CHCH₂CONHOH), 3.85 (t, 2H, CH₂OPh), 4.2 (d, 1H, NCH), 6.6 (overlapping t and s, 3H, ArH), 7.09 (t, 1H, ArH)

15

EXAMPLE 19

(2S)-N-2'-[(2'R)-2'-(carboxymethyl)-6'-(3-
methylphenoxy)hexanoyllamino-3,3-dimethylbutanoic acid N-
20 methylamide

Synthesis using a procedure analogous to that of example 13 results in a compound having the following analysis.

25 ^1H NMR (CD₃OD) δ 0.97 (s, 9H, t-butyl), 1.36-1.8 (m, 6H, (CH₂)₃), 2.25 (s, 3H, PhCH₃), 2.4-2.59 (dd, 2H, CH₂COOH), 2.64 (s, 3H, NCH₃), 2.84 (m, 1H, CHCH₂CONHOH), 3.9 (t, 2H, CH₂OPh), 4.2 (d, 1H, NCH), 6.68 (overlapping t and s, 3H, ArH), 7.09 (t, 1H, ArH)

30

The potency of compounds of the present invention to act as inhibitors of the MMPs is determined by using recombinant MMPs as follows.

35 Human cDNA for fibroblast collagenase and fibroblast stromelysin is obtained (Goldberg, G.I., Wilhelm, S.M., Kronberger, A., Bauer,

E.A., Grant, G.A., and Eisen, A.Z. (1986) J. Biol. Chem. 262, 5886-9). Human cDNA for neutrophil collagenase is obtained (Devarajan, P., Mookhtiar, K., Van Wart, H.E. and Berliner, N. (1991) Blood 77, 2731-2738). The MMPs are expressed in E.coli as inclusion bodies with the expression vector pET11a (Studier, F.W., Rosenberg, A.H. Dunn, J.J., and Dubendorff, J.W. (1990) Methods in Enzymology 185, 60-89). Fibroblast stromelysin and neutrophil collagenase are expressed as mature enzymes with C-terminal truncations, Phe83-Thr260 and Met100-Gly262, respectively. Fibroblast collagenase is expressed as a proenzyme with a C-terminal truncation, Met1-Pro250. Inclusion bodies are solubilized in 6 M urea, purified by ion exchange, and folded into their native conformation by removal of urea. Fibroblast collagenase is activated by incubation with p-aminophenylmercury. All active MMPs are purified by gel filtration.

MMPs are assayed with peptide substrates based on R-Pro-Leu-Ala-Leu-X-NH-R₂, where R=H or benzoyl, X=Trp or O-methyl-Tyr, R₂=Me or butyldimethylamino. The product is determined by fluorescence after reaction with fluorescamine with overall conditions and procedures similar to those of Fields, G.B., Van Wart, H.E., and Birkedal-Hansen, H. (1987) J. Biol. Chem. 262, 6221.

In the following table K_i values are micromolar and are calculated from the measured percent inhibition using the K_m value, and assuming competitive inhibition. HFS is Human Fibroblast Stromelysin. HFC is Human Fibroblast Collagenase. HNC is Human Neutrophil Collagenase.

Compound of

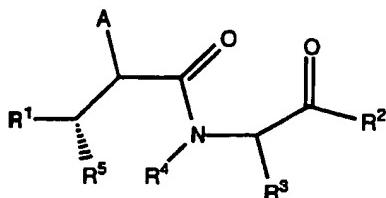
Example	HFS	HFC	HNC
2	0.015	1.45	<0.002
3	2.19	0.03	0.007
4	14.56	3.35	0.270
5	0.378	5.10	<0.002
6	1.50	0.15	0.020
8	0.057	1.4	0.005
9	5.00	0.027	0.017
10	0.044	2.27	0.21
11	0.019	0.92	0.004
12	0.70	1.6	0.120
13	0.028	0.008	---
14	0.014	0.026	---
15	0.026	0.035	0.016
16	0.017	0.014	---
17	0.009	0.021	---
19	0.22	1.8	---

Although this invention has been described with respect to specific modification, the details thereof are not to be construed as limitations, for it will be apparent that various equivalents, changes and modifications may be restored and modification may be resorted to without departing from the spirit and scope thereof and it is understood that such equivalent embodiments are intended to be included therein.

CLAIMS

1- A compound of the formula:

5



wherein

10 A is A¹ - A²- A³

A¹ is C₁-10 alkyl, C₂-10 alkene, C₂-10 alkyne having C₁-5 in the backbone or a chemical bond;

15 A² is X - Y- Z; wherein

X is a chemical bond, -O--NH-, or -S-;

Y is -CO-, or -CHR⁹;

20 Z is -O-, -NH-, -S-, or a chemical bond;

A³ is

hydrogen,

25 C₁-6 alkyl,

substituted C₁-6 alkyl,

aryl,

substituted aryl,

heteroaryl,

30 substituted heteroaryl,

heterocyclic,

substituted heterocyclic,
aryl C₁-6 alkyl,
substituted aryl C₁-6 alkyl,
heterocyclic C₁-6 alkyl,
heteroaryl C₁-6 alkyl,
substituted heteroaryl C₁-6 alkyl, or
substituted heterocyclic C₁-6 alkyl;

5

with the proviso that

- (a) at least one of X, Y and Z must contain a heteroatom;
- 10 (b) when Y is -CH₂-, then only one of X and Z can be a heteroatom;
- (c) when Y is -CO- and both X and Z are heteroatoms, then one must be -NH- and the other -NH- or -O-;
- 15 (d) when A¹ is alkyl, X is -O- or -S-, Y is CHR⁹ and Z is a chemical bond, then A³ cannot be H or C₁-6 alkyl;
- (e) when A¹ is alkyl, X is a chemical bond, Y is CHR⁹ and Z is -O- or -S-, then A³ cannot be C₁-6 alkyl;
- 20 (f) when A¹ is a chemical bond, X is O or S, Y is CH₂, and Z is a chemical bond, then A³ cannot be aryl or aryl C₁-6 alkyl;
- (g) when A¹ is a chemical bond, X is a chemical bond, Y is CO, and Z is O, then A³ cannot be H, alkyl, aryl, aryloxyalkyl, alkanoyloxyalkyl or aroyloxyalkyl; or
- 25 (h) when A¹ is a chemical bond, X is a NH, Y is CH₂, and Z is a chemical bond, then A³ cannot be alkyl, aryl, arylalkyl, cycloalkyl, or cycloalkyl alkyl;

R¹ is

- 30 HN(OH)CO-
- HCON(OH)-,
- CH₃CON(OH)-,
- HO₂C-,
- HS-, or
- phosphinate;

35

R² is

OR⁶ or NR¹⁰R⁶

where R⁶ is

hydrogen,

5 C₆-12 aryl, or

(CH₂)_nR⁷,

wherein R⁷ is

hydrogen,

phenyl,

10 substituted phenyl,

hydroxy,

C₁-6 alkoxy,

C₂-7 acyloxy,

C₁-6 alkylthio,

15 phenylthio,

sulfoxide of a thio,

sulfone of a thio,

carboxyl,

(C₁-6 alkyl) carbonyl,

20 (C₁-6 alkoxy) carbonyl,

(C₁-6 alkyl)aminocarbonyl,

arylaminoacarbonyl,

amino,

substituted acyclic amino,

25 heterocyclic amino,

N-oxide of an amine, or

C₂-7 acylamino, and

n is 1 to 6; or

R³ and R⁶ taken together are a group of the formula -(CH₂)_m-

30 where m is from 5 to 12, optionally interrupted by a NR⁸

group

where R⁸ is selected from

hydrogen,

C₁-6 alkyl,

35 C₁-6 alkylcarbonyl,

C₁-6 alkoxycarbonyl,
aryl,
aralkyl, or
aralkyloxycarbonyl,
5 in each of which the aryl moiety is optionally substituted;

R³ is a characterizing group of an alpha amino acid

C₁-6 alkyl,
C₃-10 cycloalkyl,
10 aryl methylene,
substituted aryl methylene,
C₃-10 cycloalkyl methylene
aryl,
substituted aryl,
15 fused bicycloaryl methylene,
fused substituted bicycloaryl methylene,
conjugated bicycloaryl methylene, or
conjugated substituted bicycloaryl methylene;

20 R⁴ is hydrogen or C₁-4 alkyl;

R⁵ is

hydrogen,
phenyl,
25 substituted phenyl,
amino,
hydroxy,
mercapto,
C₁-4 alkoxy,
30 C₁-6 alkylamino,
C₁-6 alkylthio,
C₁-6 alkyl or C₂-6 alkenyl,
optionally substituted by
alkyl,
35 phenyl,

substituted phenyl,
heterocyclic,
substituted heterocyclic,
amino,
5 acylated amino,
protected amino,
hydroxy,
protected hydroxy,
mercapto,
10 protected mercapto,
carboxy,
protected carboxy, or
amidated carboxy;

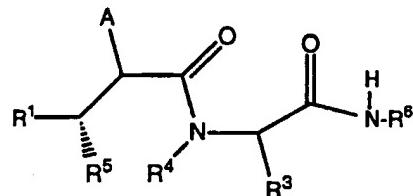
15 R⁹ is hydrogen or C₁-4 alkyl;

R¹⁰ is hydrogen or C₁-4 alkyl;

and the salts, solvates and hydrates thereof.

20

2- A compound of the structure:



25

wherein

A is A¹- A²- A³

wherein

A¹ is (CH₂)_n, and n is 3 - 5,

30 A² is X-Y-Z,

wherein,

X is a chemical bond or -NH-;

Y is -(C=O)-, -CH₂-, -(CHCH₃)-,

Z is -O-, -NH-, or a chemical bond; and

A³ is

5 hydrogen, methyl, ethyl, propyl, butyl, pentyl, phenyl,
 methylphenyl, chlorophenyl, methoxyphenyl,
 phenylmethylen, methoxyphenylmethylen,
 methylphenylmethylen, or phenylethylen.

R¹ is

10 HN(OH)CO-, or HO₂C-,

R³ is

tertiary butyl,

phenylmethylen,

15 cyclohexyl methylen, or

3,5 dimethyl phenylmethylen;

R⁴ is independently hydrogen or methyl;

20 R⁵ is

hydrogen, methyl, 2-methylpropyl, 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl or tertiary butyl; and

R⁶ is

25 methyl, 2-pyridylethylen, phenylethylen, 4-sulfamoyl
 phenylethylen, or morpholino-N-ethylen.

3- A compound of claim 2

wherein A is

- (CH₂)₄-O-H,

30 - (CH₂)₃-C=O-O-H,

- (CH₂)₃-C=O-NH-(CH₂)₂CH₃,

- (CH₂)₃-C=O-NH-(CH₂)₂- phenyl,

- (CH₂)₃-CH(CH₃)-O-H,

- (CH₂)₄-NH-C=O-(CH₂)₂CH₃,

35 - (CH₂)₄-O-phenyl,

- (CH₂)₄-O-(4-chlorophenyl),

- (CH₂) 4-O-(3-methylphenyl),
- (CH₂) 4-O-(4-methoxyphenyl),
- (CH₂) 4-O-(4-methylphenyl),
- (CH₂) 5-O-phenyl,
5 - (CH₂) 4-O-CH₂-phenyl,
- (CH₂) 5-O-CH₂-(4-methylphenyl), or
- (CH₂) 3-O-CH₂-(4-methylphenyl).

10 4- A compound of claim 3 being:

- a/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-5-(carboxy)pentanoyl]-L-phenylalanine N-methylamide;
b/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;
15 c/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(propylamino)-6-(oxo)hexanoyl]-L-phenylalanine N-methylamide;
d/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-(6RS)-6-(hydroxy)heptanoyl]-L-phenylalanine N-methylamide;
20 e/ (2S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(hydroxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
f/ (2S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid
25 N-methylamide;
g/ N-[(2'R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(4'-oxobutylamino)hexanoyl]-L-phenylalanine N-methylamide;
h/ 2(S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
30 i/ N-[(2R)-2-[(1'S)-1'-(Methyl)-2'-(hydroxyamino)-2'-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;
j/ N-[(2R)-2-[(1'S)-1'-(Methyl)-2'-(hydroxyamino)-2'-(oxo)ethyl]-6-(oxo)-6-(propylamino)hexanoyl]-L-phenylalanine
35 N-methylamide;

- k/ (2S)-N-2[(2'R)-[(1"R)-1''-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl-2''-(hydroxyamino)-2''-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
- 5 l/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(oxo)-6-(propylamino)hexanoyl]-L-phenylalanine N-2-phenylethylamide;
- m/ (2S)-N-2-[(2'R)-2'-[(1"S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;
- 10 n/ (2S)-N-2-[(2'R)-2'-[(1"S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6'- (oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;
- o/ (2S)-N-2-[(2'R)-2'-[(1"S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6'- (oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;
- 15 p/ (2S)-N-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'- (phenylmethoxy)hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4'-sulfamoyl)phenylethylamide;
- 20 q/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6'- (phenylmethoxy)hexanoyl]-L-(3,5-dimethyl)phenylalanine N-2-(4'-sulfamoyl)phenylethylamide;
- r/ (2S)-N-2'-[(2'R)-2'-[2''-(hydroxyamino)-2''-(oxo)ethyl]-6'- [(4-methoxy)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;
- 25 s/ (2S)-N-2'-[(2'R)-2'-[2''-(hydroxyamino)-2''-(oxo)ethyl]-6'- [(4-methyl)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;
- t/ (2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'- [(1-oxo)butylamino]hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4'-sulfamoyl)phenylethylamide;
- 30 u/ (2S)-N-2-[(2'R)-2'-[(1"S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6- (phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;
- 35 v/ (2S)-N-2-[(2'R)-2'-[(1"S)-1''-(2-Methylpropyl)-2''-(hy-

- droxyamino)-2"--(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-
amino-3,3-dimethylbutanoic acid N-methylamide;
- w/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenoxy)-
hexanoyl]-L-phenylalanine N-methylamide;
- 5 x/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-7-(phenoxy)-
heptanoyl]-L-phenylalanine N-methylamide;
- y/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid
N-2-phenylethylamide;
- 10 z/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid
N-2-(4'-sulfamoyl)phenylethylamide;
- aa/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-5-(phenyl-
methoxy)pentanoyl]-L-phenylalanine N-methylamide;
- 15 ab/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-7-(phenyl-
methoxy)heptanoyl]-L-phenylalanine N-methylamide;
- ac/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenyl-
oxy)hexanoyl]-L-phenylalanine N-methylamide;
- ad/ N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-7-[(phenyl-
oxy)heptanoyl]-L-phenylalanine N-methylamide;
- 20 ae/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(2-phenethylamino)-6'(oxo)hexanoyl]amino-3,3-
dimethylbutanoic acid N-methylamide;
- af/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(4-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic
acid N-methylamide;
- 25 ag/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(4-chlorophenoxy)hexanoyl]amino-3,3-dimethylbutanoic
acid N-methylamide;
- ah/ (2S)-N-2'-[(2'R)-2'-[2"--(Hydroxyamino)-2"--(oxo)ethyl]-6'-
[(3-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic
acid N-methylamide; and
- ai/ (2S)-N-2'-[(2'R)-2'-(carboxymethyl)-6'-(3-
methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-
methylamide.

- 5- A pharmaceutical composition comprising an effective amount of a compound of claim 1.
- 6- A pharmaceutical composition comprising an effective amount of a compound of claim 2.
- 7- A pharmaceutical composition comprising an effective amount of a compound of claim 3.
- 10 8- A pharmaceutical composition comprising an effective amount of a compound of claim 4.
- 15 9- A method of promoting an antiarthritic effect in a mammal in need thereof comprising administering thereto a matrix metalloproteinase inhibitory effective amount of a compound of claim 1.
- 20 10- A method of promoting an antiarthritic effect in a mammal in need thereof comprising administering thereto a matrix metalloproteinase inhibitory effective amount of a compound of claim 2.
- 25 11- A method of promoting an antiarthritic effect in a mammal in need thereof comprising administering thereto a matrix metalloproteinase inhibitory effective amount of a compound of claim 3.
- 30 12- A method of promoting an antiarthritic effect in a mammal in need thereof comprising administering thereto a matrix metalloproteinase inhibitory effective amount of a compound of claim 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/02249

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,091,024 (ONDETTI) 23 MAY 1978, ENTIRE DOCUMENT.	1-12
A,P	US, A, 5,304,549 (BROADHURST ET AL) 19 APRIL 1994, ENTIRE DOCUMENT.	1-12

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See patent family annex.

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"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&"	document member of the same patent family

Date of the actual completion of the international search

25 APRIL 1995

Date of mailing of the international search report

01 JUN 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/02249

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/15, 31/16, 31/165, 31/17, 31/19, 31/195, 31/215, 31/224, 31/265;
C07C 233/05, 233/16, 233/24, 233/30.

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

564/47, 53, 153, 155, 159, 162, 163, 164, 165, 168, 169, 170; 558/ 253, 254, 256, 257; 560/251; 514/513,
561, 563, 568, 588, 597, 616, 618, 619, 625.

B. FIELDS SEARCHED

Minimum documentation searched
Classification System: U.S.

564/47, 53, 153, 155, 159, 162, 163, 164, 165, 168, 169, 170; 558/ 253, 254, 256, 257; 560/251; 514/513,
561, 563, 568, 588, 597, 616, 618, 619, 625.

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